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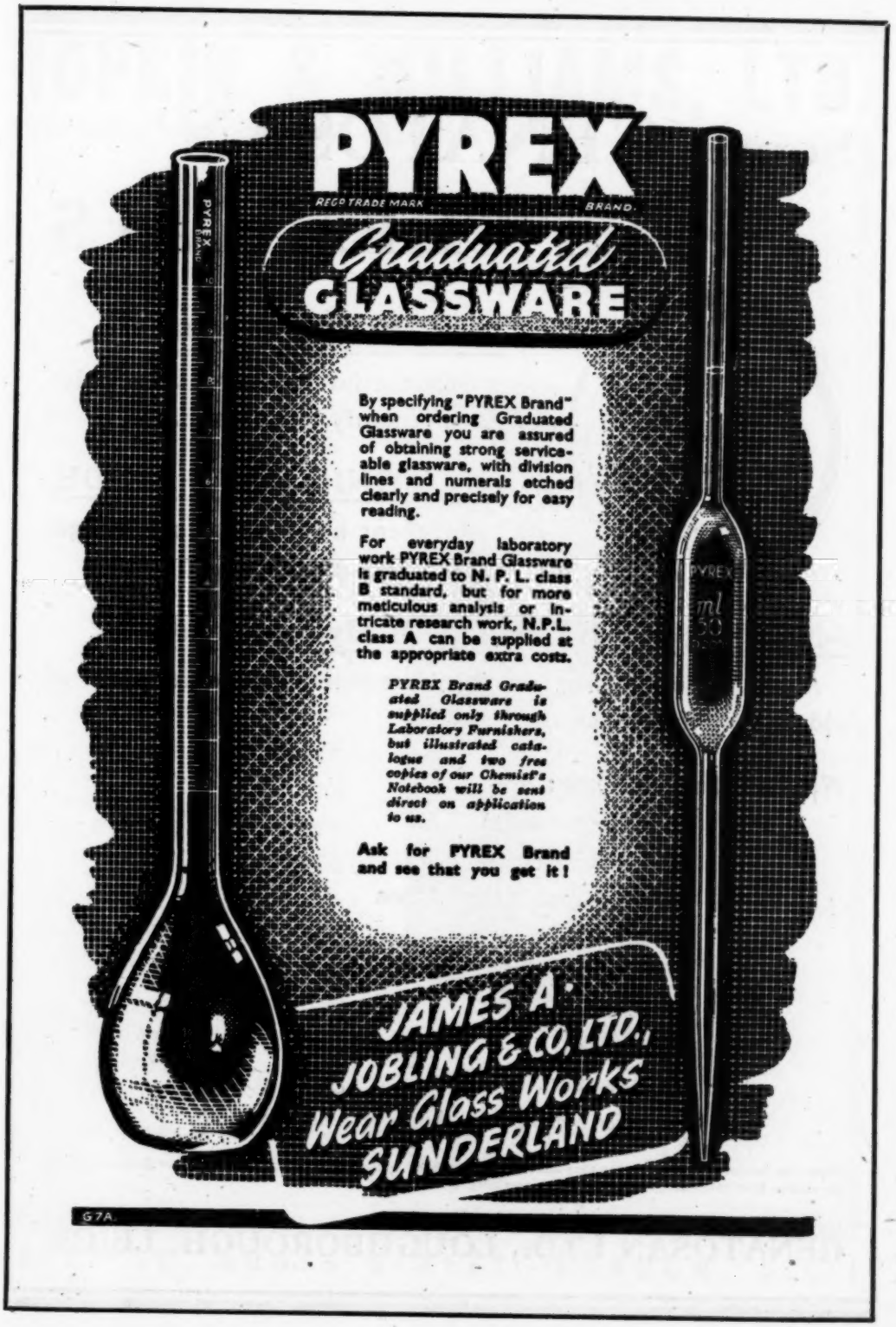
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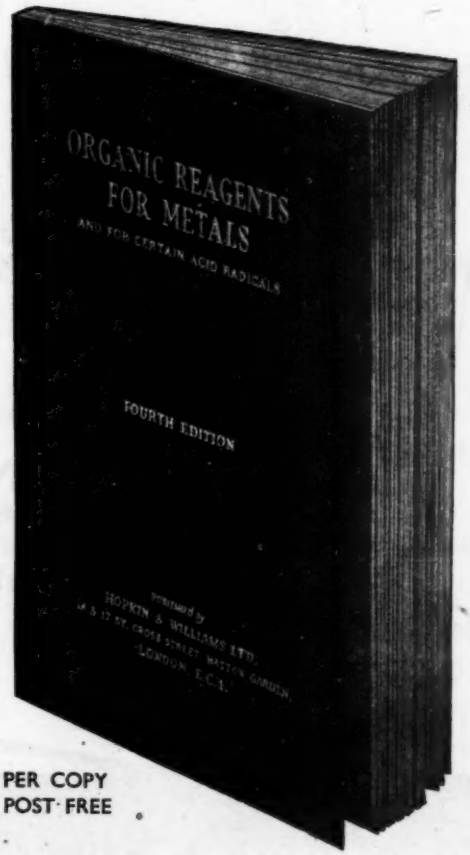

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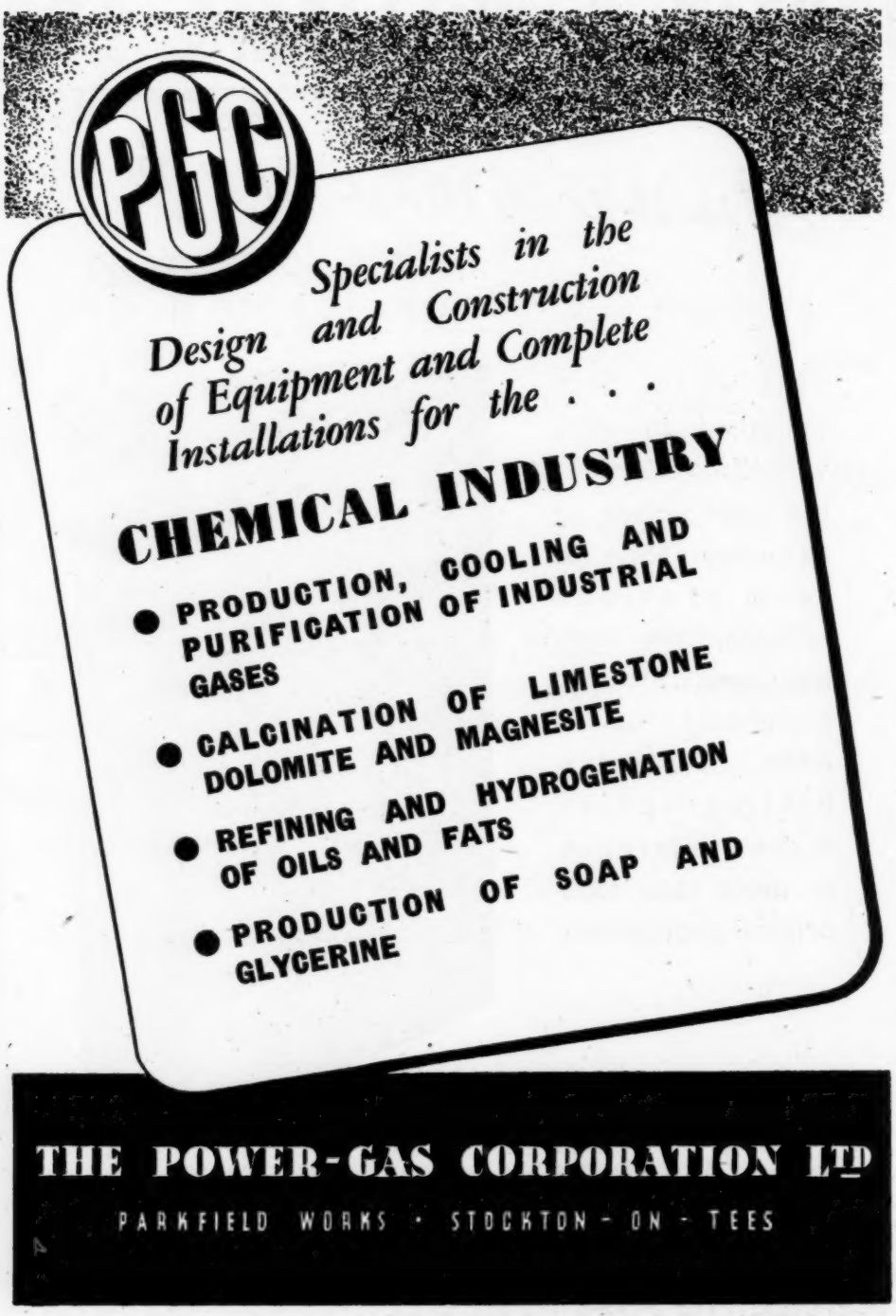
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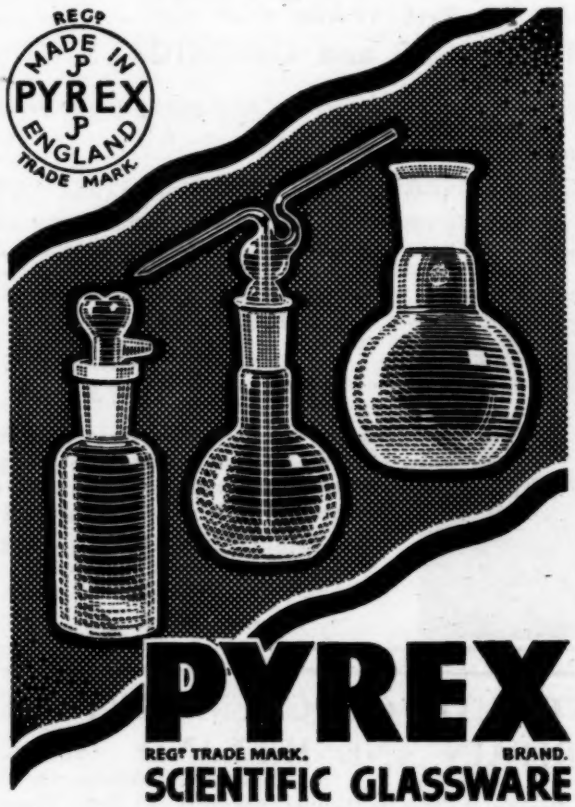

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½ hr. with a mixture of ethyl alcohol (20 c.c.) and 50% aqueous sulphuric acid (20 c.c.); the red solid (1·6 g.) deposited on cooling was filtered off, washed with aqueous ethyl alcohol, dried, and, after three crystallisations from ethyl alcohol containing 40% of acetone, obtained in scarlet prisms of 4 : 6-*dinitro*-1-*naphthylamine*, m. p. 178° (Found : N, 17·95. $C_{10}H_7O_4N_3$ requires N, 18·0%). Another sample of the crude red hydrolysed product (1·8 g.) was dissolved in glacial acetic acid (30 c.c.) and diazotised by addition below 20° to a solution of sodium nitrite (0·65 g.) in sulphuric acid (10 c.c., *d* 1·84); the diazo-solution was added to a suspension of cuprous oxide (3·0 g.) in methyl alcohol (35 c.c.), nitrogen being evolved and the temperature rising to 56°. When the evolution of nitrogen had ceased, a further quantity of cuprous oxide (3·0 g.) was added, the mixture stirred for 5 mins., poured into iced water (400 c.c.), and the precipitate filtered off, washed, dried, and refluxed for 1 hour with ethylene dichloride (50 c.c.). The filtered extract was evaporated to 5 c.c. (charcoal), filtered, diluted with ligroin, and the yellow precipitate (0·5 g.) crystallised three times from 90% acetic acid; pale orange needles (0·1 g.) of a mixture of 1 : 7- and 2 : 6-dinitronaphthalenes (m. p. 136—174°) were obtained (Found : N, 12·9. Calc. : N, 12·8%). This mixture was sublimed at 200—220°/10—15 mm., and the orange solid obtained was fractionally sublimed at 10—15 mm. as follows : (i) for 2 hrs., at 180°, giving a pale orange-yellow solid; (ii) at 200°, all but a few mg. of the solid being obtained as a bright orange-yellow compound. The residual few mg. were sublimed separately (iii) as stout orange needles of 2 : 6-dinitronaphthalene, m. p. 278°, mixed m. p. with an authentic specimen kindly supplied by Prof. W. P. Wynne, 278—279° (Chatt and Wynne, this vol., p. 35, give m. p. 279°). Sublimate (i) was resublimed at 165—170°/10—15 mm., and the first crop (ia) of very pale orange-yellow needles had m. p. 144—147·5°; the remainder (*ca.* 5%), collected at 175°, proved to be 2 : 6-dinitronaphthalene. Crop (ia) was resublimed as follows : the first crop collected during 5 mins. at 175° was rejected, and the main crop (*ca.* 70%) was collected at 160° during 2 hours as creamy-white needles of 1 : 7-dinitronaphthalene, m. p. 148—149°, raised to 156° by repeated sublimations (Veselý and Dvorák, *Bull. Soc. chim.*, 1923, **33**, 319, give m. p. 156°).

Further Nitration of 6-*Nitroaceto*-1-*naphthalide*.—The naphthalide (5·1 g.) was stirred into nitric acid (35 c.c., *d* 1·5) below 3°, the stirring continued for 5 mins., the mixture poured on ice (400 g.) and kept for 1 hour, and the precipitate (5·6 g.) filtered off, washed, and dried in a vacuum. It was hydrolysed by 2 hours' refluxing on the water-bath with ethyl alcohol (55 c.c.) and 50% sulphuric acid (55 c.c.); on cooling, a deep red solid (4·1 g.) consisting mainly of 4 : 6-dinitro-1-naphthylamine separated; the mother-liquors on dilution with ice gave an orange-yellow solid (0·37 g.), which crystallised from aqueous acetone in deep yellow needles of 2 : 6-*dinitro*-1-*naphthylamine*, m. p. 226·5—228·5° (Found : N, 17·35. $C_{10}H_7O_4N_3$ requires N, 18·0%). The crude 4 : 6-dinitro-compound was crystallised four times from ethyl alcohol containing 10% of acetone and deaminated, but the product was a mixture of 2 : 6- with 1 : 7-dinitronaphthalene as the chief constituent, from which the former was obtained by recrystallisation of the vacuum-sublimed product three times from 90% pyridine, once from glacial acetic acid, and finally from 90% pyridine; it crystallised in creamy-white needles, m. p. 274—275°, mixed m. p. with an authentic sample 277°.

Nitration of 6-*Nitro*-p-*toluenesulphon*-1-*naphthalide*.—This naphthalide (2·5 g.) was dissolved in glacial acetic acid (25 c.c.), and treated at 60° with 7·5 c.c. of a solution of nitric acid (1 c.c., *d* 1·5, in 9 c.c. of glacial acetic acid); the mixture was heated at 90° for 5 mins. and then allowed to cool, whereupon 2 : 4 : 6-*trinitro*-p-*toluenesulphon*-1-*naphthalide* set to a mass of fine cream needles (1·65 g.), which were filtered off, and washed with glacial acetic acid, methyl alcohol, and light petroleum; it crystallised from glacial acetic acid in cream needles, m. p. 172·5° (Found : N, 13·1. $C_{17}H_{12}O_8N_4S$ requires N, 12·9%). 2 : 4 : 6-*Trinitro*-1-*naphthylamine* was formed when the above naphthalide (1·25 g.) was stirred into cold sulphuric acid (5 c.c., *d* 1·84), the mixture heated at 40° for 5 mins., and poured on ice; the orange-red amine which separated (0·72 g.) crystallised from pyridine in deep yellow, felted needles, m. p. 301—304° (decomp. begins at *ca.* 280°) (Found : N, 20·1. $C_{10}H_6O_6N_4$ requires N, 20·15%).

Mercuration of 6-*Nitro*-1-*naphthylamine*.—The amine (5·0 g.), dissolved in boiling glacial acetic acid (30 c.c.), was added to a hot solution of mercuric acetate (8·6 g.) in glacial acetic acid (15 c.c.), and the mixture boiled for 5 mins., cooled, and filtered; the precipitate (8·5 g.) of 6-*nitro*-1-*naphthylamine*-4-*mercuriacetate* crystallised from glacial acetic acid (charcoal) in silvery-white prisms, m. p. above 400° (Found : Hg, 44·1. $C_{12}H_{10}O_4N_2Hg$ requires Hg, 44·9%).

4-*Iodo*-6-*nitro*-1-*naphthylamine* was obtained when the above mercuriacetate (2·5 g.), made into a paste with 20% aqueous potassium iodide (20 c.c.), was heated on the water-bath during addition of a solution of iodine (1·45 g.) in 20% aqueous potassium iodide (20 c.c.); after a further ½ hr.'s heating, the mixture was cooled, the crude 4-iodo-6-nitro-1-naphthylamine (0·75 g.) filtered off, washed with water and dilute sodium thiosulphate, and crystallised from aqueous alcohol containing 15% of acetone (charcoal), forming bright red needles, m. p. 175° (Found : N, 9·1; I, 40·0. $C_{10}H_7O_2N_2I$ requires N, 8·9; I, 40·4%).

The above amine (2·1 g.), dissolved in glacial acetic acid (10 c.c.), was diazotised by addition with stirring below 20° to a solution of sodium nitrite (0·7 g.) in sulphuric acid (3 c.c., *d* 1·84), and the cold diazo-solution added to one of cuprous bromide (3·0 g.) in 20% hydrobromic acid (60 c.c.); after an hour, the mixture was poured on ice, the crude 1-*bromo*-4-*iodo*-6-*nitronaphthalene* filtered off, dried in a vacuum, extracted with acetone (charcoal), and the extract concentrated; the resulting dull fawn-coloured solid was sublimed at 180—190°/10—15 mm., and the scaly yellow sublimate crystallised from acetone, forming lemon-yellow needles, m. p. 130·5—131·5° (Found : N, 3·8. $C_{10}H_5O_2NBrI$ requires N, 3·7%).

Synthesis of 1-*Bromo*-2-*iodo*-6-*nitronaphthalene*.—1-Bromo-6-nitro-*p*-toluenesulphon-2-naphthalide (3·0 g.) was hydrolysed and diazotised as previously described, excess of nitrous acid removed by urea, and the solution added to one of potassium iodide (30 g.) in water (50 c.c.); the temperature rose to 40°, and was taken to 50° to complete the reaction. Ice was then added, free iodine removed by dilute sodium thiosulphate, and the 1-*bromo*-2-*iodo*-6-*nitronaphthalene* (1·6 g.) filtered off, washed, and dried in a vacuum; it crystallised first from acetone and then from aqueous acetic acid (charcoal) in clusters of yellow needles, m. p. 193—194° (Found : N, 3·85. $C_{10}H_5O_2NBrI$ requires N, 3·7%).

Coupling of Diazotised p-*Toluidine with* 6-*Nitro*-1-*naphthylamine*.—*p*-Toluidine (1·71 g.) was heated with hydrochloric acid (6·5 c.c., *d* 1·16) and sufficient water to dissolve the hydrochloride when the mixture was hot. The cooled solution was diazotised by addition of sodium nitrite (1·2 g.) dissolved in a little water, excess of nitrous acid removed by urea, and the diazo-solution stirred gradually at −5° into a solution of 6-nitro-1-naphthylamine (3·0 g.) in ethyl alcohol (160 c.c.), the stirring being continued for ½ hr.; the mixture was then heated to 20°, and a slight excess of saturated aqueous sodium acetate added. The crude 6-*nitro*-4-p-*tolueneazo*-1-*naphthylamine* (3·05 g.) was filtered off, washed with water, dried at 50°, and crystallised from toluene, forming deep maroon boat-shaped crystals; from benzene it afforded very deep maroon clusters of micro-needles, m. p. 242·5° (Found : N, 18·2. $C_{17}H_{14}O_2N_4$ requires N, 18·3%). The *acetyl* derivative crystallised from glacial acetic acid (charcoal) in felted orange needles, m. p. 300—301° (Found : N, 16·3. $C_{19}H_{16}O_3N_4$ requires N, 16·1%).

6-*Nitro*-4-p-*tolueneazonaphthalene*-1-*azoresorcinol*.—The above aminoazo-compound (1·5 g.) was dissolved in glacial acetic acid (50 c.c.), hydrochloric acid (2·0 c.c., *d* 1·16) added at 8°, and then, gradually, solid sodium nitrite (0·5 g.). After 0·2 g. had been added, the temperature rose rapidly to 12° and was maintained there during the addition. The clear orange-red solution of the diazo-compound was stirred for ½ hr. and then added at 10° to a solution of resorcinol (0·7 g.) in 20% aqueous sodium hydroxide (225 c.c.), mixed with ice (200 g.). Coupling ensued and the mixture was kept for 2 hrs., then heated to 50°, and the dye (1·23 g.) removed, washed, and dried in a vacuum; it was obtained as a deep violet-black solid with a greenish-gold reflex, which was purified by repeated dissolution in hot cellosolve (20 c.c., charcoal)

and precipitation by light petroleum (100 c.c.) until no ash was left after ignition on platinum foil; m. p. >400° (Found: N, 16·8. Calc. for $C_{23}H_{17}O_4N_5$: N, 16·4%); the dye gave a deep blue colour with concentrated sulphuric acid in contrast to the behaviour of the previous monoazo-dye, which afforded an orange-pink colour.

Note.—Deaminations by Hodgson and Turner's cuprous oxide–alcohol method (J., 1942, 748) are best carried out with methyl alcohol (rather than with ethyl alcohol), the yields being improved and the formation of troublesome ester avoided.

The authors thank I.C.I. (Dyestuffs) Ltd. for several micro-analyses and for gifts of chemicals.

TECHNICAL COLLEGE, HUDDERSFIELD. [*Received, April 12th,* 1943.

NOTE.

Preparation of the Œstrogen β-Bromo-β-phenyl-αα-di-(p-ethoxyphenyl)ethylene. By WADIE TADROS and A. SCHÖNBERG.

THIS œstrogen, the remarkably prolonged action of which when given orally has been reported by Robson, Schönberg, and Tadros (*Nature*, 1942, **150**, 22; the name of the last author was inadvertently omitted in this publication) was prepared as follows: To the Grignard reagent prepared from magnesium (14 g.), benzyl chloride (85 g.), and ether (400 c.c.), 4 : 4'-diethoxybenzophenone (95 g.) was added, and after 2 hours' stirring, the solution was left overnight and then decomposed with cold aqueous ammonium chloride. Benzene–ether extracted *di-(p-ethoxyphenyl)benzylcarbinol*, which separated from petroleum (b. p. 100—110° or 100—150°) in colourless crystals, m. p. 124°, in almost theoretical yield (Found: C, 80·0; H, 7·0. $C_{24}H_{26}O_3$ requires C, 79·5; H, 7·2%). *β-Phenyl-αα-di-(p-ethoxyphenyl)ethylene*, obtained in almost theoretical yield by the vacuum distillation of the carbinol (50 g.) in presence of 1 drop of 20% sulphuric acid (the distillation was effective only when the substance, which turned violet on heating, became almost colourless), separated from alcohol in colourless crystals, m. p. 74° (Found: C, 83·6; H, 6·6. $C_{24}H_{24}O_2$ requires C, 83·7; H, 7·0%). *β-Bromo-β-phenyl-αα-di-(p-ethoxyphenyl)ethylene* was prepared by adding a solution of bromine (37 g.) in glacial acetic acid (50 c.c.) to a solution of the ethylenic compound (80 g.) in the same solvent (200 c.c.) and refluxing the mixture for 45 minutes. The bromo-compound, which separated on cooling, was recrystallised from glacial acetic acid, methyl alcohol, or alcohol, forming almost colourless or very pale yellow crystals, m. p. 97—98°. Yield, about 90% (Found: C, 67·9; H, 5·5; Br, 18·5. $C_{24}H_{23}O_2Br$ requires C, 68·1; H, 5·5; Br, 18·9%).—FOUAD I UNIVERSITY, CAIRO, EGYPT. [*Received, April 16th,* 1943.]

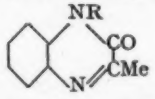
104. *Quinoxaline Cyanines. Part II.*

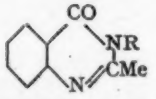
By A. H. COOK and C. A. PERRY.

3-Keto-2-methyl-3 : 4-dihydroquinoxaline and its 4-*N*-methyl and -phenyl compounds give quaternary salts by addition to the basic nitrogen atom in the 1-position. In these salts the 2-methyl group is reactive and has been condensed with a variety of formic acid derivatives and aldehydes or equivalent compounds to give symmetrical and unsymmetrical oxygenated cyanines.

Except for diminished solubility these dyes resemble those derived from true quinoxalines, particularly in their deep blue colour.

EARLIER workers have prepared cyanines from a variety of heterocyclic compounds containing reactive methyl groups. The cyanines now described differ, however, from previous examples in that the parent compounds contain an oxygenated ring system of type (I).

(I.) 

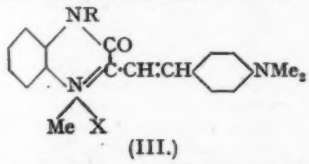
 (II.)

The closest previous approach to dyes of this class is the attempt of Bogert and Clark (*J. Amer. Chem. Soc.*, 1924, **46**, 1294) to utilise the quinazolone ring system (II) as the basis of cyanine dyes. These workers obtained coloured condensation products, but no true cyanines, from the methiodide of (II, R = H) and dimethylaminobenzaldehyde. The dyes now described are derived from dihydroketoquinoxalines and thus bear the same relation to those described in Part I (J., 1942, 710) as Bogert and Clark's suggested compounds would bear to the quinazoline cyanines of Heilbron and his co-workers (J., 1932, 251). Incidentally preliminary experiments showed that the quaternary salts of (II, R = H) give brilliant colours with 1 : 3 : 3-trimethyl-2-methyleneindoline-ω-aldehyde, so the quinazolone cyanines can probably be obtained with the aid of more recent intermediates.

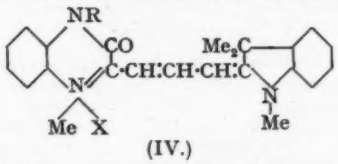
(I, R = H) is available in almost theoretical yield from *o*-phenylenediamine and cold aqueous pyruvic acid (Hinsberg, *Annalen*, 1896, **292**, 245). The *N*-methyl compound (I, R = Me) has been obtained by methylation with diazomethane (Ohle, Gross, and Wolter, *Ber.*, 1937, **70**, 2148); in our experience it is obtainable more conveniently by methylating the parent compound with methyl sulphate in alkaline solution. *N*-Ethylation was less satisfactory and *N*-benzylation could not be effected under moderate conditions. Unlike true quinoxalines (I) contains two dissimilar nitrogen atoms; one bears an acidic hydrogen atom and the other permits the formation of quaternary salts. When (I, R = H) was heated with methyl iodide at 100°, formation of methiodide was too slow to be useful; moreover, on prolonged heating, the crude product reacted with diphenylformamidine to give a dye under conditions which were successful with (I, R = Me) but not with the unmethylated compound quaternised in other ways, so *N*-methylation was also taking place. The *N*-methyl compound gave a well-defined *monomethiodide* and a similar quaternary salt was prepared from (I, R = Ph). Pure methiodides were, however, unnecessary for subsequent condensations; these were

successfully carried out by converting the parent bases into metho- or etho-sulphates, which were used without further purification. It was concluded that no appreciable *N*-alkylation of (I, R = H) occurred under the conditions employed, for it was shown that the products did not show the same behaviour as salts from *N*-substituted derivatives of (I, R = H).

In these quaternary salts the 2-methyl group is reactive, as it is in quinaldine quaternary salts and similar compounds. The crude methosulphate (I, R = H) condensed at once in a mixture of pyridine and acetic anhydride with *p*-dimethylaminobenzaldehyde or with 1 : 3 : 3-trimethyl-2-methyleneindoline-ω-aldehyde to give the dyes (III) and (IV) (R = H). Both the methosulphate and the ethosulphate of (I, R = H) condensed



(III.)



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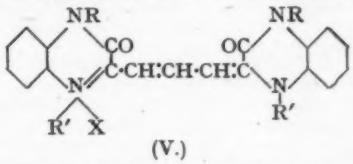
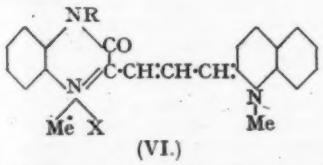


(V.)

rapidly with diphenylformamidine in the same medium to give the symmetrical compounds (V; R = H, R′ = Me or Et).

To extend the series to further unsymmetrical cyanines it was decided to utilise anilinovinyl derivatives of the second heterocyclic nucleus. Attempts to prepare anilinovinyl derivatives from quaternary salts of the dihydroquinoxalones (I; R = H, Me, or Ph) were fruitless, as were also attempts to obtain 2-ω-methylene aldehydes from the same quaternary salts, phosphorus oxychloride, and methylformanilide; approaches through this type of intermediate were therefore abandoned.

When anilinovinyl compounds such as those derived from quaternary salts of quinaldine, 2-methylbenzoxazole, or 2-methylbenzthiazole and crude dihydroquinoxalone quaternary salts were used, difficulties similar to those encountered in Part I were experienced. However, on boiling the appropriate reactants with excess of anhydrous sodium acetate in acetic anhydride, relatively good yields of the dyes (VI—VIII; R = H) were obtained:



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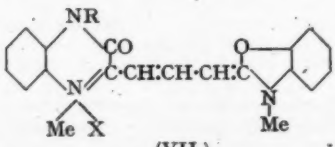
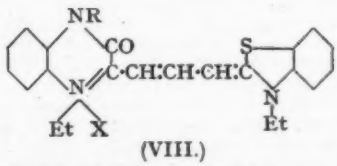
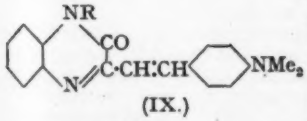


(VII.)



(VIII.)

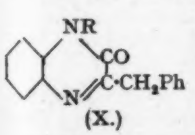
Turning to (I, R = Me), both its pure methiodide and crude metho- and etho-sulphate preparations condensed very readily with *p*-dimethylaminobenzaldehyde or with 1 : 3 : 3-trimethyl-2-methyleneindoline-ω-aldehyde to give *N*-methyl analogues of (III) and (IV). On prolonged heating in acetic anhydride (less satisfactorily in absence of solvent but with the aid of zinc chloride) (I, R = Me) condensed with *p*-dimethylaminobenzaldehyde to the brick-red cyanine base (IX, R = Me). This combined at once with methyl sulphate in neutral solvents to give an intensely coloured solution spectroscopically identical with the cyanine prepared directly from the methosulphate. It gave also intensely coloured solutions with mineral acids (cf. Hamer, J., 1940, 799). A base (IX, R = Ph) showing similar behaviour was obtained from the phenyl analogue. Though it was later found that quaternary salts of (I, R = Me) condense surprisingly well with diphenylformamidine to give the *N*-methyl analogue of (V), the condensation could not be satisfactorily effected under the ordinary conditions nor was the preparation of the symmetrical dye successful when ethyl orthoformate or sodium formate was used in the usual media. The *N*-methyl analogue of (V) was, however, obtained remarkably cleanly by boiling the methosulphate of (I, R = Me) in alcoholic solution with ethyl orthoformate, preferably in presence of a little concentrated sulphuric acid. The yields were maximal after only 5 minutes' boiling. Some colour was produced in absence of quaternising agent, but the yield of dye under these conditions was very small. When the quaternary salts of (I, R = Me) were heated with 2-anilinovinyl- or 2-methylanilinovinyl-benzthiazole meth- or eth-iodide in acetic anhydride containing excess of anhydrous sodium acetate, the *N*-methyl analogue of (VIII) was obtained; the formation of colours, probably due to (VI) and VII (R = Me), was also observed.



(IX.)

(I, R = Ph) was quaternised with methyl or ethyl sulphate, and the crude salts condensed with other intermediates as in the case of the *N*-methyl compound. In this way *N*-phenyl analogues of the dyes (III—VIII) were prepared, usually in excellent yield.

2-Keto-3-benzyl-1 : 2-dihydroquinoxaline (X, R = H) was obtained from phenylpyruvic acid and *o*-phenylenediamine. Methylation with methyl sulphate in alkaline solution afforded (X, R = Me); this constitution rather than an *O*-methyl structure is probable from the similar reaction described earlier. Lastly, condensations of phenylpyruvic acid with *o*-aminodiphenylamine gave (X, R = Ph). These quinoxalines gave colours after quaternisation and condensation with *p*-dimethylaminobenzaldehyde or 1 : 3 : 3-trimethyl-2-methyleneindolinealdehyde. The dyes were, however, less stable than those with an unsubstituted polymethin chain and they were not closely examined.



(X.)

Some attempts were made to condense suitable quinoxaline quaternary salts with glutacondialdehyde dianil. Intensely coloured solutions were invariably obtained, but the instability of the dyes, presumably quinoxaline tricarbocyanines, defeated attempts to isolate them.

All the dyes described here bear a general resemblance to the true quinoxaline cyanines of Part I. The colours tend to fade in dilute solution and are reversibly discharged by alkali. The dyes were uniformly less soluble than their non-oxygenated analogues. More remarkable, however, is the fact that in most of them the marked bathochromic influence of the quinoxaline system can be traced as it can in the non-oxygenated compounds. Thus solutions are generally blue or blue-green, showing strong absorption in the red region of the spectrum.

Experimental.

[2-(3-*Hydroxy*-1-*methylquinoxaline*)][(4-*dimethylaminophenyl*)]*dimethincyanine Iodide* (III; R = H, X = I).—3-Hydroxy-2-methylquinoxaline (1 g.) was heated at 140° with methyl sulphate (0·6 c.c.) for 5—10 minutes, cooled, and the excess of methyl sulphate removed by washing with ether. The residue was treated with *p*-dimethylaminobenzaldehyde (1 g.) and acetic anhydride (10 c.c.), and the whole boiled for 15 minutes. The green solution was treated with water (50 c.c.) and excess of potassium iodide. The *iodide* of the dye was collected after some hours, washed with much water, and extracted with ether. The residue (1·45 g.) crystallised from alcohol and a little water in small feathery needles, m. p. 225—227° (Found: N, 9·5. $C_{19}H_{20}ON_3I$ requires N, 9·4%). Light absorption (alcohol): max., 6070 A.

[2-(3-*Keto*-1-*methyl*-3 : 4-*dihydroquinoxaline*)][2-(1 : 3 : 3-*trimethylindoline*)]*trimethincyanine Iodide* (IV; R = H, X = I).—The ketodihydroquinoxaline (1 g.) was quaternised with methyl sulphate (0·6 c.c.) at 140° for 15 minutes, and the product treated with trimethylmethyleneindoline-ω-aldehyde (1·25 g.) in acetic anhydride (8 c.c.) and pyridine (5 c.c.). After 2 hours at room temperature water (20 c.c.) and potassium iodide were added; the *dye* was washed with ether and crystallised from 50% alcohol. The yield was poor (Found: I, 25·8. $C_{23}H_{24}ON_3I$ requires I, 26·2%). Light absorption (alcohol): max., 6290, 5860, 5460 A.; II, III > I.

[*Bis*-2-(3-*hydroxy*-1-*methylquinoxaline*)]*trimethincyanine Acetate* (V; R = H, R′ = Me, X = O·CO·CH_3).—3-Hydroxy-2-methylquinoxaline (2 g.) was quaternised as in earlier experiments. The crude methosulphate was treated with acetic anhydride (10 c.c.), diphenylformamidine (1·25 g.), and lastly with pyridine (10 c.c.); heat was evolved. The solution was allowed to cool slowly; on dilution with water the dye was precipitated as a green deposit (2 g.). It was the *acetate* and crystallised from acetic acid in well-defined needles, m. p. 280° (decomp.) (Found: N, 13·4. $C_{23}H_{22}O_4N_4$ requires N, 13·4%). Light absorption (alcohol): max., 6390, 5880 A.; I > II.

[2-(3-*Keto*-1-*methyl*-3 : 4-*dihydroquinoxaline*)][2-(1-*methylquinoline*)]*trimethincyanine Iodide* (VI; R = H, X = I).—3-Hydroxy-2-methylquinoxaline (5 g.) was quaternised as usual with methyl sulphate (3·4 c.c.) and then boiled with 2-anilinovinylquinoline methiodide (6 g.), anhydrous sodium acetate (12 g.), and acetic anhydride (25 c.c.) for 15 minutes. The solution was decomposed with water, and the practically insoluble *iodide* (9 g.) crystallised from acetic acid, in which it gave a violet solution; m. p. 246° (Found: N, 8·8. $C_{22}H_{20}ON_3I$ requires N, 8·9%). Light absorption (alcohol): max., 5930, 5520 A.; I > II.

[2-(3-*Hydroxy*-1-*methylquinoxaline*)][2-(1-*methylbenzoxazole*)]*trimethincyanine Iodide* (VII; R = H, X = I).—2-Methylbenzoxazole methiodide (2 g.), diphenylformamidine (1·45 g.), and acetic anhydride (10 c.c.) were boiled for 20 minutes, and the solution then added with anhydrous sodium acetate (3 g.) to 3-hydroxy-2-methylquinoxaline (1·2 g.) quaternised in the usual manner with methyl sulphate (2 c.c.). The whole was boiled for 10 minutes, and the deep red dye (1·7 g.) precipitated with water. The *iodide*, crystallised from acetic acid, had m. p. 244° (Found: N, 9·1. $C_{20}H_{18}O_2N_3I$ requires N, 9·1%). Light absorption (alcohol): max., 6350, 5560, 5220 A.; II, III > I.

[2-(3-*Hydroxy*-1-*ethylquinoxaline*)][2-(1-*ethylbenzthiazole*)]*trimethincyanine Iodide* (VIII; R = H, X = I).—2-Methylbenzthiazole ethiodide (2 g.) was boiled for 20 minutes with acetic anhydride (10 c.c.) and diphenylformamidine (1·25 g.). To the solution were added 3-hydroxy-2-methylquinoxaline (1·2 g.), previously quaternised with ethyl sulphate (2 c.c.) in the usual manner, acetic anhydride (5 c.c.), and anhydrous sodium acetate (5 g.) and the whole was boiled for 10 minutes. The *iodide* (3·1 g.) was centrifuged after precipitation with water and potassium iodide. It separated from alcohol, in which it gave a magenta solution, as a powder, m. p. 260°. The recovery on crystallisation was poor (Found: I, 24·5. $C_{22}H_{22}ON_3IS$ requires I, 24·7%). Light absorption (alcohol): max., 5940, 5550 A.; II > I.

2-*Keto*-1 : 3-*dimethyl*-1 : 2-*dihydroquinoxaline* (I, R = Me).—3-Hydroxy-2-methylquinoxaline (50 g.), dissolved in 5% aqueous potassium hydroxide (600 c.c.), was treated with methyl sulphate (32 c.c.) with shaking in the cold. The clear solution on standing deposited the *N*-methyl compound (50 g.) in the pure state, identical with the product obtained by using diazomethane (Ohle, Gross, and Wolter, *loc. cit.*) or *via* *N*-methyl-*o*-phenylenediamine and pyruvic acid (Kehrmann and Messinger, *Ber.*, 1892, **25**, 1627). It was distilled at atm. pressure, b. p. 306°. The *methiodide* was obtained by heating the quinoxaline (2 g.) with methyl iodide (10 c.c.) at 100° for 48 hours. The crystalline mass was extracted thoroughly with ether and the residual, pale brown crystals were recrystallised from alcohol (charcoal); the methiodide separated in needles, m. p. 178° (decomp.) (Found: I, 39·9. $C_{11}H_{13}ON_2I$ requires I, 40·3%).

[2-(3-*Keto*-1 : 4-*dimethyldihydroquinoxaline*)][(4-*dimethylaminophenyl*)]*dimethincyanine Sulphate* (III; R = Me, X = SO_4).—2-Keto-1 : 3-dimethyl-1 : 2-dihydroquinoxaline (1 g.) was quaternised with methyl sulphate at 180° for 4 minutes, and *p*-dimethylaminobenzaldehyde (0·8 g.) in acetic anhydride (4 c.c.) added to the cooled product, followed by pyridine (1 c.c.). The reaction mixture soon became semi-solid and after a few minutes the dye was collected and washed with ether (2 g.). The *methosulphate* crystallised in green needles from methyl alcohol (Found: N, 9·8. $C_{21}H_{25}O_5N_3S$ requires N, 9·7%). Light absorption (alcohol): max., 6350, 6270 A.; II > I.

The cyanine *base* (IX, R = Me) was obtained by refluxing 2-keto-1 : 3-dimethyl-1 : 2-dihydroquinoxaline (1 g.) with *p*-dimethylaminobenzaldehyde (0·85 g.) in acetic anhydride (16 c.c.) for 8 hours. After cooling, the mixture was decomposed with water and basified. The light brown base (1·5 g.) crystallised from alcohol in brick-red needles, m. p. 186° (Found: N, 13·4. $C_{19}H_{19}ON_3$ requires N, 13·8%).

[2-(3-*Keto*-1 : 4-*dimethyldihydroquinoxaline*)][2-(1 : 3 : 3-*trimethylindoline*)]*trimethincyanine Chloride* (IV; R = Me, X = Cl).—The quinoxaline (1 g.) was heated at 180° for 50 minutes with methyl sulphate (2 c.c.), the mixture cooled, and acetic anhydride (4 c.c.) added, followed by 1 : 3 : 3-trimethyl-2-methyleneindoline-ω-aldehyde (1·2 g.) in pyridine (2 c.c.). The mixture was heated just to boiling and allowed to cool overnight. Water (250 c.c.) and sodium chloride were added, and the whole warmed on the steam for some hours. The *chloride* (1·1 g.) separated on cooling. After recrystallising from dilute acetic acid, it had m. p. 135° (Found: N, 10·0; Cl, 8·5. $C_{24}H_{26}ON_3Cl$ requires N, 10·3; Cl, 8·7%). Light absorption (alcohol): max., 6350, 5920, 5500 A.; II, III > I.

[2-*Bis*-(3-*keto*-1 : 4-*dimethyldihydroquinoxaline*)]*trimethincyanine Sulphate* (V; R = R′ = Me, X = SO_4).—(*a*) 2 Keto-1 : 3-dimethyl-1 : 2-dihydroquinoxaline (5 g.) was quaternised with methyl sulphate at 180° for 4 minutes, and the product boiled with methyl alcohol (20 c.c.), ethyl orthoformate (6 c.c.), and concentrated sulphuric acid (2 drops) for 5 minutes. The *methosulphate* (1·5 g.) was precipitated with water and crystallised from methyl alcohol containing a little sulphuric

acid; m. p. 227° (Found: N, 11·1. $C_{24}H_{26}O_6N_4S$ requires N, 11·2%). Light absorption (alcohol): max., 6520, 5980 A.; I > II. (*b*) The quinoxaline (17·4 g.) was quaternised with methyl sulphate (12·6 g.), and acetic anhydride (54 c.c.) added to the crude product, followed by diphenylformamidine (9·8 g.) and pyridine (10 c.c.), with cooling. When the reaction had subsided, the product was diluted with ether and the dye (12·8 g.) collected. It formed a lustrous green powder, from which a little tarry material could be extracted with warm benzene. On crystallisation from methanol a product identical with that prepared previously was obtained.

[2-(3-*Keto*-4-*methyl*-1-*ethyldihydroquinoxaline*)][2-(1-*ethylbenzthiazole*)]*trimethincyanine Iodide*.—2-Keto-1 : 3-dimethyldihydroquinoxaline (2·6 g.) was quaternised with ethyl sulphate (3 c.c.) at 180° for 4 minutes and then added to a solution prepared by boiling diphenylformamidine (1·47 g.) and 2-methylbenzthiazole ethiodide (4·6 g.) with acetic anhydride (20 c.c.) for 20 minutes. The whole was boiled for a few minutes, water added, and the oily dye caused to solidify by warming with aqueous potassium iodide (yield, 3 g.). The *iodide* was crystallised from alcohol acidified with a little hydrogen iodide; m. p. 180° (Found: N, 7·9. $C_{23}H_{24}ON_2IS$ requires N, 8·1%). Light absorption (alcohol): max., 5560, 5150 A.; I > II.

2-*Keto*-1-*phenyl*-3-*methyl*-1 : 2-*dihydroquinoxaline* (I, R = Ph).—This was best prepared by adding pyruvic acid to an equivalent amount of *o*-aminodiphenylamine dissolved in ether; slight heat was evolved. After evaporation of the solvent the residual orange solid crystallised from alcohol in pale yellow needles, m. p. 195° (cf. Kehrmann and Messinger, *Ber.*, 1892, **25**, 1628).

[2-(3-*Keto*-4-*phenyl*-1-*methyldihydroquinoxaline*)][(4-*dimethylaminophenyl*)]*dimethincyanine Chloride* (III; R = Ph, X = Cl).—2-Keto-1-phenyl-3-methyldihydroquinoxaline (5 g.) was heated with methyl sulphate (10 c.c.) at 180° for 4 minutes. The liquid was cooled, and acetic anhydride (20 c.c.) added, followed by *p*-dimethylaminobenzaldehyde (3·25 g.). The mixture was just heated to boiling, and water (250 c.c.) and excess of sodium chloride added. The green-bronze *chloride* was crystallised repeatedly from alcohol containing a little hydrochloric acid; m. p. 198—199° (Found: N, 9·9. $C_{25}H_{24}ON_3Cl$ requires N, 10·1%). Light absorption (alcohol): max., 6370 A.

The cyanine *base* (IX, R = Ph), prepared in the same way as the *N*-methyl analogue described above, separated as a brick-red crystalline powder, m. p. 210°, from alcohol (Found: N, 11·3. $C_{24}H_{21}ON_3$ requires N, 11·4%).

The corresponding 3-keto-4-phenyl-1-ethyldihydroquinoxaline dye was obtained in exactly similar manner from ethyl sulphate. 5 G. of the keto-compound afforded 8 g. of crude *chloride*, which was crystallised from alcohol containing hydrochloric acid; m. p. 281° (Found: N, 9·9. $C_{26}H_{26}ON_3Cl$ requires N, 9·8%). Light absorption (alcohol): max., 6500 A.

[2-(3-*Keto*-4-*phenyl*-1-*methyl*-3 : 4-*dihydroquinoxaline*)][2-(1 : 3 : 3-*trimethylindoline*)]*trimethincyanine Chloride* (IV; R = Ph, X = Cl).—The ketodihydroquinoxaline (1 g.) was quaternised at 180° for 30 minutes with methyl sulphate (2 c.c.) and then treated successively with acetic anhydride (4 c.c.), trimethylmethyleneindoline aldehyde (1 g.), and pyridine (3 c.c.). The whole was refluxed for 30 minutes, and hot water and excess of sodium chloride added. The *chloride* separated (1·6 g.) and was crystallised from dilute acetic acid; it had m. p. 252° (Found: Cl, 7·4. $C_{29}H_{28}ON_3Cl$ requires Cl, 7·6%). Light absorption (alcohol): max., 6530, 5950, 5540 A.; II > I > III.

[*Bis*-2-(3-*keto*-4-*phenyl*-1-*methyldihydroquinoxaline*)]*trimethincyanine Sulphate* (V; R = Ph, R′ = Me, X = SO_4).—3-Keto-4-phenyl-2-methyldihydroquinoxaline (5 g.) was quaternised as before with methyl sulphate. The product was dissolved in methyl alcohol (20 c.c.), 2 drops of concentrated sulphuric acid added, and the whole refluxed with ethyl orthoformate (6 c.c.) for 5 minutes. The *sulphate* was precipitated by water and crystallised from methyl alcohol containing sulphuric acid; m. p. 287° (Found: N, 8·8. $C_{24}H_{20}O_6N_4S$ requires N, 9·0%). Light absorption (alcohol): max., 6560, 6020 A.; I > II. The dye was red in alcohol but became blue on addition of acid.

[2-(3-*Keto*-4-*phenyl*-1-*methyl*-3 : 4-*dihydroquinoxaline*)][2-(1-*methylquinoline*)]*trimethincyanine Sulphate* (VI; R = Ph, X = SO_4).—2-Methylanilinovinylquinoline methiodide (3·8 g.) was shaken with aqueous sodium carbonate and benzene until all solid had disappeared. The benzene solution was filtered, dried, and evaporated. The residue, dissolved in pyridine (4 c.c.), was added to 3-keto-4-phenyl-2-methyldihydroquinoxaline methosulphate (prepared from 2·4 g. of quinoxaline) in acetic anhydride (6 c.c.); much heat was evolved. After cooling, the *sulphate* (1·8 g.) was collected, washed with ether, and crystallised from glacial acetic acid, forming small green needles, m. p. 244° (decomp.) (Found: S, 6·4. $C_{29}H_{27}O_5N_3S$ requires S, 6·5%). It gave purple solutions in the common solvents. Light absorption (alcohol): max., 6560 A.

[2-(3-*Keto*-4-*phenyl*-1-*methyl*-3 : 4-*dihydroquinoxaline*)][2-(1-*methylbenzthiazole*)]*trimethincyanine Chloride* (as VIII; R = Ph, X = Cl).—2-Methylanilinovinylbenzthiazole methiodide (2 g.) was treated with sodium carbonate and benzene as in the preceding preparation. The residue from the benzene extract was dissolved in pyridine (3 c.c.) and added to 3-keto-4-phenyl-2-methyldihydroquinoxaline (1·2 g.) which had been quaternised with methyl sulphate and dissolved in acetic anhydride (4 c.c.). Heat was evolved; after cooling, the mixture was decomposed with water and salted out with sodium chloride. The *chloride* was obtained as a dark red powder (0·8 g.) crystallising from dilute acetic acid; it had m. p. 235° (decomp.) (Found: Cl, 7·2. $C_{26}H_{22}ON_3ClS$ requires Cl, 7·2%). Light absorption (alcohol): diffuse band, max., *ca.* 5500 A.

2-*Keto*-3-*benzyl*-1 : 2-*dihydroquinoxaline* (X, R = H).—Phenylpyruvic acid (Erlenmeyer and Arbenz, *Annalen*, 1904, **333**, 228) (8·2 g.) in concentrated alcoholic solution was added to *o*-phenylenediamine (5 g.) also in alcoholic solution. The *quinoxaline* separated as a dense precipitate within a few seconds. It crystallised from alcohol in small needles, m. p. 196° (Found: N, 12·1. $C_{15}H_{12}ON_2$ requires N, 11·9%).

2-*Keto*-1-*phenyl*-3-*benzyl*-1 : 2-*dihydroquinoxaline* (X, R = Ph).—*N*-Phenyl-*o*-phenylenediamine (9·2 g.) and phenylpyruvic acid (8·2 g.) were condensed by mixing ethereal solutions of the reactants. The crude product (15 g.) obtained on evaporating the solvent crystallised from glacial acetic acid in needles, m. p. 166° (Found: N, 8·9, 9·1. $C_{21}H_{16}ON_2$ requires N, 9·0%). This and the preceding compound behaved qualitatively like other quinoxalines but the cyanine dyes rapidly disappeared and so were not isolated.

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105. *Quinoxaline Cyanines. Part III.*

By A. H. COOK and R. F. NAYLOR.

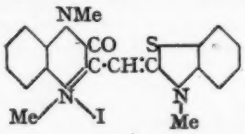
Two quinoxalinemonomethincyanines have been obtained, but attempts to extend the series by modifying procedures which are satisfactory in other heterocyclic systems had no success.

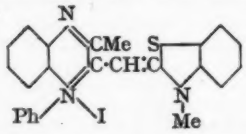
Several quinoxalines carrying reactive methyl groups have been condensed with ethyl oxalate, and the resulting pyruvic esters or acids converted into diquinoxalinylmethanes by reaction with aromatic *o*-diamines. Although it was not possible to quaternise these compounds and so obtain monomethincyanines, the stability of

the diquinoxalinylmethanes is of interest and the striking colours of their acid solutions are probably indicative of the colour of the cyanines, which still remain to be prepared.

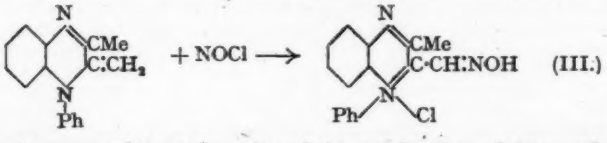
QUINOXALINETRIMETHINCYANINES have already been prepared (Part I, J., 1942, 710) and it was desirable to see whether the bathochromic influence of quinoxaline nuclei extended to monomethincyanines.

The dye (I) was obtained very readily from quaternised 3-keto-2 : 4-dimethyl-3 : 4-dihydroquinoxaline and the methiodide of 2-benzthiazyl methyl sulphide. A similar reaction with 1-phenyl-3-methyl-2-methylene-1 : 2-dihydroquinoxaline gave two products in small yield, one the dye (II), the other unidentified.

(I.) 

 (II.)

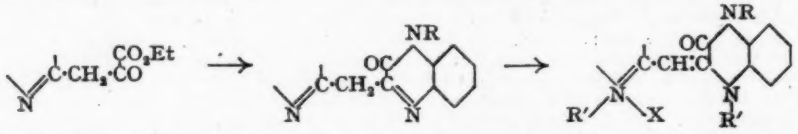
Quinoxaline salts or the corresponding methylene bases were found to react readily with nitrosyl chloride to give oxime salts (cf. B.P. 359,753). We were, however, unsuccessful in condensing (III) with a second quinox-

 (III.)

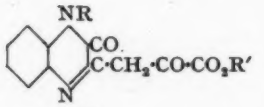
aline or other heterocyclic quaternary salt, nor in spite of the production of deep red colours could any pure cyanine be obtained by a similar single-stage process without isolation of (III). A related procedure using amyl nitrite (D.R.-P. 459,616) was no more satisfactory.

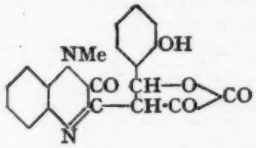
The two quinoxaline cyanines prepared were red, whereas other known monomethincyanines are much paler, so here also the quinoxaline system is strongly bathochromic.

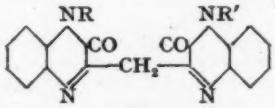
Quinaldine and similar compounds carrying a reactive methyl group condense with ethyl oxalate to give substituted pyruvates (Wislicenus and Kleisinger, *Ber.*, 1897, **30**, 1479; 1909, **42**, 1141; cf. Borsche and co-workers, *Annalen*, 1936, **526**, 22; 1938, **534**, 56; 1939, **537**, 39). We hoped to utilise such pyruvates to obtain substituted methanes and thence by quaternisation to prepare quinoxalinemonomethincyanines :



2 : 3-Dimethylquinoxaline, 3-keto-2-methyl-, 3-keto-2 : 4-dimethyl-, and 3-keto-4-phenyl-2-methyl-dihydroquinoxaline were condensed with ethyl oxalate and potassium ethoxide in presence of pyridine to give the expected pyruvic esters rapidly and in excellent yield. The constitution of these products was placed beyond doubt by the reactions of the typical ester (IV; R = Me, R′ = Et). Thus when its potassio-derivative was boiled with ethanol, and the solution just acidified, the free acid (IV, R′ = H) was obtained. Again, the ester contained both a carbonyl and a reactive methylene group and was characterised as its salicylaldehyde condensation product and its *oxime*; the former was not the stilbene derivative but the *lactone* (V), the pyruvates

 (IV.)

 (V.)

 (VI.)

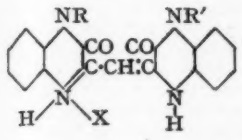
studied by Borsche yielding similar products. No success attended attempts to condense 3-keto-2-methyl-dihydroquinoxaline with ethyl oxalate. Similar non-reactivity of the NH-compound compared with *N*-alkyl homologues in this reaction has been noted by Borsche and his co-workers. Failure must also be recorded of attempts to use α-picoline, 4 : 5-diphenyl-2-methyliminazole, and 1-phenyl-3-methyl-5-pyrazolone in this reaction, though 4 : 5-diphenyl-2-methyloxazole behaved normally and gave a pyruvic ester.

The acid (IV; R = Me, R′ = H) or its ester reacted with *o*-phenylenediamine in absence of solvent at 180° to give the *compound* (VI; R = Me, R′ = H), less satisfactorily obtained by condensation in alcoholic hydrochloric acid. This compound reacted exceedingly slowly with diazomethane, but the symmetrical N-*methyl* compound (VI; R = R″ = Me) was prepared by condensing (IV; R = Me, R′ = Et) with *N*-methyl-*o*-phenylenediamine. Finally, reaction of (IV; R = Me, R′ = H), but not its ester, with *o*-aminodiphenylamine and a trace of ammonium chloride at 150° afforded (VI; R = Me, R′ = Ph). The reaction failed even on much stronger heating when ammonium chloride was omitted; later it was found that this condensation and other similar ones proceeded exceedingly well in fused phenol.

By similar means (IV; R = Ph, R′ = Et) was condensed with *o*-phenylenediamine and *N*-methyl-*o*-phenyl-

enediamine to give (VI; R = Ph, R′ = H and Me, respectively). The identity of the products from *N*-methyl-*o*-phenylenediamine with (VI; R = Me, R′ = Ph) above provided proof of the constitutions suggested.

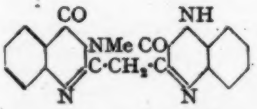
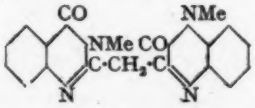
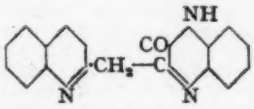
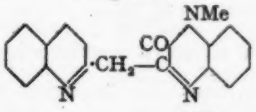
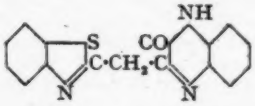
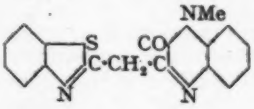
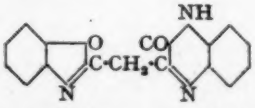
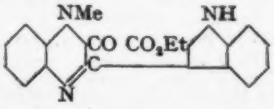
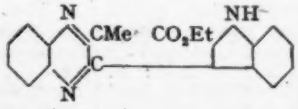
Many attempts were made to quaternise compounds of type (VI), even boiling methyl sulphate or *p*-toluenesulphonate alone or in nitrobenzene as diluent being tried. In every case intense colours were observed, but these were destroyed on dilution with water and the original compounds were recovered. The colours appear to be due to salts formed with a small amount of free acid, for they were paralleled by colours in sulphuric acid. All dissolved in concentrated acid to give relatively pale solutions which became intensely coloured on dilution or warming. The colours, shown in the table, disappeared on addition of much water and the original diquinoxalinylmethanes were precipitated if the treatment with acid had not been too drastic.



When both heterocyclic nuclei were quinoxaline (oxygenated or non-oxygenated), the disubstituted methanes were extraordinarily stable in concentrated sulphuric acid, retaining in boiling solutions their brilliant blue or permanganate colour without a trace of carbonisation occurring. These colours, it is suggested, are due to salts which may be compared with monomethincyanines. The bases dissolved in alcoholic hydrogen chloride to give similar deep colours and from the solutions dark solids could be precipitated with ether; the composition of these indicated them to be monohydrochlorides.

The table includes further compounds with a variety of heterocyclic systems. In obtaining the derivatives of quinazoline, advantage was taken of the reactivity of the *C*-methyl group in 2 : 3-dimethyl-4-quinazolone to convert this compound into the corresponding pyruvic ester; most of the others were obtained by the methods developed above; the indole derivatives were prepared by the Fischer method from the phenylhydrazones of the appropriate pyruvic esters.

None of the compounds containing one quinoxaline nucleus except the indoles gave such characteristic intense colours in sulphuric acid as the diquinoxalinylmethanes. After being heated with sulphuric acid, the colour of the diquinoxalinylmethanes gave place to a weaker but still bright orange on addition of water or alkali; sulphonation alone seemed to have occurred. When glycerol was added to the sulphuric acid solution in the hot, the red colour gave place to an equally intense blue-green, but these colours were less stable and soon disappeared with carbonisation.

Compound.	Colour of solid.	Colour in hot sulphuric acid.
(VI; R = Me, R′ = H)	Scarlet	Crimson to violet
(VI; R = Me, R′ = Ph)	Orange	Magenta
(VI; R = Ph, R′ = H)	Orange	Magenta
(VI; R = R′ = Me)	Scarlet	Violet
(VI; R = R′ = Ph)	Orange	Magenta
	Orange-red	Blue
	Orange	Blue
	Yellow	Pale yellow
	Pale orange	Pale yellow
	Crimson-red	Light red
	Red	Light red
	Light orange	Orange
	Yellow	Orange
	Dull yellow	Orange
	Dull yellow	Blue-red
	Buff	Deep blue-maroon

Experimental.

[2-(1-*Methylbenzthiazole*)][2-(3-*keto*-1 : 4-*dimethyl*-3 : 4-*dihydroquinoxaline*)]*monomethincyanine Iodide* (I).—2-Keto-1 : 3-dimethyl-1 : 2-dihydroquinoxaline (1 g.) was quaternised by heating with methyl sulphate (2 c.c.) at 180° for 30 mins., 2-methylbenzthiazyl sulphide methiodide (1·85 g.) and pyridine (15 c.c.) added, and the whole boiled for 10 minutes. The *iodide* (1·65 g.) crystallised from acetic acid in orange-red needles, m. p. 242°, which were only slightly soluble in acetone or ethanol (Found: C, 48·6; H, 3·7; N, 9·0; I, 27·3. $C_{19}H_{18}ON_2IS$ requires C, 49·2; H, 3·7; N, 9·1; I, 27·5%).

[2-(1-*Methylbenzthiazole*)][2-(1-*phenyl*-3-*methylquinoxaline*)]*monomethincyanine Iodide* (II).—*o*-Aminodiphenylamine (1·5 g.) and diacetyl (0·75 g.) were condensed in cold ethereal solution. The solvent was removed, the methylene base

diluted with ethanol (10 c.c.), 2-methylbenzthiazyl sulphide methiodide (2·6 g.) added, and the whole boiled for 10 mins. The *iodide*, which separated on cooling and contained a more soluble, unidentified compound, crystallised from ethanol in small red needles, m. p. 188° (Found: C, 56·8; H, 4·2. $C_{24}H_{20}N_2IS$ requires C, 56·5; H, 3·9%).

1-*Phenyl*-3-*methylquinoxaline*-2-*aldoxime Chloride* (III).—*o*-Aminodiphenylamine (4·5 g.) and diacetyl (2·2 g.) were condensed in absence of solvent and the methylene base was dissolved in carbon tetrachloride and added to nitrosyl chloride (1 mol.) in cold carbon tetrachloride. After some hours the *chloride* was collected; it crystallised from ethanol, on addition of ether, in small brown needles, m. p. 283° (Found: N, 14·3. $C_{16}H_{14}ON_3Cl$ requires N, 14·0%).

To the solution prepared from potassium (7·5 g.) in ethanol (36 c.c.) was added 2-keto-1 : 3-dimethyldihydroquinoxaline (17·4 g.) dissolved in pyridine (90 c.c.), followed by ethyl oxalate (13 c.c.). The mixture reddened and set solid almost at once. The liquid was decanted, the potassio-compound washed with ether and shaken with 10% hydrochloric acid (60 c.c.), and the orange ester collected and dried at 80° (yield, 11 g.). *Ethyl* 2-*keto*-1-*methyl*-1 : 2-*dihydroquinoxaline*-3-*pyruvate* (IV; R = Me, R′ = Et) separated from ethanol in yellow needles, m. p. 170° (Found: C, 61·1; H, 5·15; N, 10·0. $C_{14}H_{14}O_4N_2$ requires C, 61·3; H, 5·1; N, 10·2%). The *oxime* (0·9 g.), prepared by refluxing the ester (1·2 g.) with hydroxylamine hydrochloride (0·75 g.) and potassium acetate (1 g.) in ether (25 c.c.) for 4 hours, crystallised from 30% ethanol in needles, m. p. 158·5° (Found: N, 14·5. $C_{14}H_{15}O_4N_3$ requires N, 14·5%). The pyruvate (1·8 g.), salicylaldehyde (0·6 c.c.), and piperidine (4 drops) were mixed in ether (5 c.c.), solvent removed by evaporation, and the residue heated at 150—170° for 1 hour. The product was boiled with ethanol (100 c.c.), and the residue crystallised from decalin–nitrobenzene (2 : 1); the *condensation product* (V) had m. p. 228° (Found: N, 8·2. $C_{19}H_{14}O_5N_2$ requires N, 8·0%). From a hot solution of the pyruvic ester (0·5 g.) and phenylhydrazine (0·25 g.) in 50% acetic acid the *phenylhydrazine* (0·6 g.) separated in orange-red crystals, m. p. 202° after recrystallisation from amyl acetate (Found: N, 15·4. $C_{20}H_{20}O_3N_4$ requires N, 15·4%). The potassio-compound of the pyruvate (2 g.) was refluxed with ethanol (25 c.c.) for 4 hours. The residue was dissolved in water, and the filtered solution acidified with 2N-hydrochloric acid. The precipitated 2-*keto*-1-*methyl*-1 : 2-*dihydroquinoxaline*-3-*pyruvic acid* (IV; R = Me, R′ = H) was purified by solution in alkali bicarbonate and reprecipitation with acid; it then had m. p. 218° and separated from 35% ethanol as an orange microcrystalline powder (Found: N, 11·6. $C_{12}H_{10}O_4N_2$ requires N, 11·4%). The same acid was obtained by acidifying the potassio-compound in the original condensation with 10% hydrochloric acid at 60°.

2-Keto-1-methyldihydroquinoxaline-3-pyruvic ester (2 g.) in hot ethanol (75 c.c.) was added to *o*-phenylenediamine (0·8 g.) in 50% ethanol (8 c.c.) and a small excess of 32% hydrochloric acid. 3-(2-*Keto*-1-*methyldihydroquinoxalinyl*)-3-(2-*ketodihydroquinoxalinyl*)*methane* (VI; R = Me, R′ = H) was precipitated on boiling and was filtered from the cooled solution (yield, 1·7 g.). It separated from aqueous pyridine in dull orange needles, m. p. 355° (Found: N, 17·7. $C_{18}H_{14}O_2N_4$ requires N, 17·7%). The same compound was obtained by heating equimolecular quantities of the pyruvic ester and *o*-phenylenediamine alone for 40 mins. at 150—170°, or with phenol (1 mol.) at 100°; the yields were quantitative. 2-Keto-1-methyldihydroquinoxaline-3-pyruvic acid (9·0 g.), *N*-methyl-*o*-phenylenediamine (4·5 g.), and phenol (3 g.) were heated at 95° for 40 mins. The product, *bis*-3-(2-*keto*-1-*methyl*-1 : 2-*dihydroquinoxalinyl*)*methane*, was ground and thoroughly extracted with hot ethanol and then with ether (yield, 10·5 g.). It separated from nitrobenzene in microcrystalline form, m. p. 331° (Found: C, 68·6; H, 4·85; N, 16·9. $C_{19}H_{16}O_2N_4$ requires C, 68·7; H, 4·8; N, 16·9%). Ketomethyldihydroquinoxalinepyruvic ester (6·3 g.), *o*-aminodiphenylamine (4·7 g.), and ammonium chloride (0·2 g.) were intimately mixed and heated for 50 mins. at 150°. The product was triturated with ethanol, and the residue (6·2 g.) recrystallised from decalin–nitrobenzene; 3-(2-*keto*-1-*methyldihydroquinoxalyl*)-3-(2-*keto*-1-*phenyldihydroquinoxalyl*)-*methane* (VI; R = Me, R′ = Ph) separated in small orange needles, m. p. 300° (Found: N, 14·0. $C_{24}H_{18}O_2N_4$ requires N, 14·2%).

2-Keto-1-phenyl-3-methyldihydroquinoxaline (25 g.) in pyridine (150 c.c.) at 60° was treated with ethyl oxalate (14 c.c.) and then with a mixture of pyridine (20 c.c.) and ethanol (39 c.c.) in which potassium (8 g.) had been dissolved. The yellow solid was collected, decomposed with cold 2N-hydrochloric acid (1500 c.c.), and the orange ester (18 g.) collected. *Ethyl* 2-*keto*-1-*phenyl*-1 : 2-*dihydroquinoxaline*-3-*pyruvate* (IV; R = Ph, R′ = Et) crystallised from ethanol in needles, m. p. 224° (Found: C, 67·5; H, 4·9; N, 8·5. $C_{19}H_{16}O_4N_2$ requires C, 67·9; H, 4·75; N, 8·3%). By acidifying the potassio-compound with warm 2N-hydrochloric acid, 2-*keto*-1-*phenyldihydroquinoxaline*-3-*pyruvic acid* (IV; R = Ph, R′ = H) was obtained; it separated from ethanol as an orange microcrystalline powder, m. p. 226° (decomp.) (Found: N, 9·1. $C_{17}H_{12}O_4N_2$ requires N, 9·1%). The ester (6·7 g.) and *o*-phenylenediamine (2·2 g.) were heated together for 30 mins. at 150° to yield 3-(2-*keto*-1-*phenyldihydroquinoxalyl*)-3-(2-*ketodihydroquinoxalyl*)*methane* (VI; R = Ph, R′ = H); this, washed with ethanol and recrystallised from nitrobenzene, formed orange needles (6 g.), m. p. 372° (Found: N, 14·4. $C_{23}H_{16}O_2N_4$ requires N, 14·7%). The ester (13·4 g.) and *N*-methyl-*o*-phenylenediamine (4·9 g.) were condensed in phenol (3 g.) as in the previous preparation. 3-(2-Keto-1-phenyldihydroquinoxalyl)-3-(2-keto-1-methyldihydroquinoxalyl)methane (VI; R = Ph, R′ = Me) was obtained (yield, 7·5 g.) identical with (VI; R = Me, R′ = Ph) described above.

Potassium (8 g.) was dissolved in ethanol (40 c.c.), the solution mixed with ether (50 c.c.) and ethyl oxalate (24 c.c.) in ether (26 c.c.) added, followed by 2 : 3-dimethyl-4-quinazolone (17·4 g.) dissolved in ethanol (35 c.c.) and ether (15 c.c.); the whole was left overnight in the cold. The yellow potassio-compound was collected and shaken for 1 hour with ice-cold 5% hydrochloric acid (120 c.c.). *Ethyl* 3-*methyl*-4-*quinazolonyl*-2-*pyruvate* (yield, 18 g.) was recrystallised from ethanol; it had m. p. 173° (Found: C, 61·3; H, 5·1; N, 10·2. $C_{14}H_{14}O_4N_2$ requires C, 61·2; H, 5·1; N, 10·2%). The *phenylhydrazone*, pale yellow needles from ethanol, had m. p. 168—169° (Found: C, 66·2; H, 5·5; N, 15·4. $C_{20}H_{20}O_3N_4$ requires C, 65·9; H, 5·5; N, 15·4%). An intimate mixture of the ester (2·8 g.) and *o*-phenylenediamine (1·4 g.) was heated at 120° for 10 mins., and the solid product twice extracted with boiling ethanol. The residual 2-(3-*methyl*-4-*quinazolonyl*)-3-(2-*ketodihydroquinoxalyl*)*methane* (3·2 g.) crystallised from nitrobenzene in long yellow needles, m. p. 354° (Found: C, 68·0; H, 4·4; N, 17·4. $C_{18}H_{14}O_2N_4$ requires C, 68·0; H, 4·4; N, 17·6%). When *N*-methyl-*o*-phenylenediamine was substituted for *o*-phenylenediamine in the preceding preparation, 2-(3-*methyl*-4-*quinazolonyl*)-3-(2-*keto*-1-*methyldihydroquinoxalyl*)*methane* was obtained; it separated from nitrobenzene–decalin (1 : 1) in long yellow needles, m. p. 293° (Found: N, 16·6. $C_{19}H_{16}O_2N_4$ requires N, 16·8%). The corresponding 2-(3-*methyl*-4-*quinazolonyl*)-3-(2-*keto*-1-*phenyldihydroquinoxalyl*)*methane* (from *o*-aminodiphenylamine) separated from nitrobenzene–decalin in yellow needles, m. p. 265° (Found: N, 14·2. $C_{24}H_{18}O_2N_4$ requires N, 14·2%).

Ethyl 3-methylquinoxaline-2-pyruvate phenylhydrazone (2·5 g.) was ground with zinc chloride (5 g.), and the mixture heated at 140° for 5 mins. The dark melt was extracted with dilute sulphuric acid, and the residue crystallised from ethanol. It was further purified by adsorbing impurities on a short column of alumina from ethanol solution, and the recovered material crystallised from light petroleum. 2-*Carbethoxy*-3-(3′-*methyl*-2′-*quinoxalyl*)*indole* had m. p. 153° (Found: N, 12·7. $C_{20}H_{17}O_2N_3$ requires N, 12·7%). 2-*Carbethoxy*-3-(2′-*keto*-1′-*methyldihydro*-3′-*quinoxalyl*)*indole*, prepared similarly from the phenylhydrazone of 2-keto-1-methyldihydroquinoxaline-3-pyruvic ester, formed fine needles, m. p. 246°, from ethyl acetate (Found: N, 11·8. $C_{20}H_{17}O_3N_3$ requires N, 12·1%).

(VI; R = Me, R′ = Ph) (1 g.) was added to a warm solution of excess of hydrogen chloride in ethanol (50 c.c.), and the filtered solution treated with dry ether (400 c.c.). 3-(2-*Keto*-1-*methyldihydroquinoxalyl*)-3-(2-*keto*-1-*phenyldihydroquinoxalyl*)*methane hydrochloride* was precipitated as a dark purple, microcrystalline powder (0·3 g.). After

drying at room temperature, it had m. p. 290° (decomp.) (Found : Cl, 8·2. $C_{24}H_{18}O_2N_4$,HCl requires Cl, 8·17%). 3-(2-*Keto*-1-*methyldihydroquinoxalyl*)-3-(2-*ketodihydroquinoxalyl*)*methane hydrochloride* was prepared by allowing a solution of the parent base (1 g.) to stand for 2 weeks with alcoholic hydrogen chloride. The solid was collected and washed with dry ether. It formed a dark purple powder (1 g.) decomposing above 300° (Found : N, 15·5; Cl, 9·2. $C_{18}H_{14}O_2N_4$,HCl requires N, 15·8; Cl, 10·0%).

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106. *New Therapeutic Agents of the Quinoline Series. Introduction and Part I. Monopyridylquinolines.*

By H. COATES, A. H. COOK, I. M. HEILBRON, D. H. HEY, A. LAMBERT, and (in part) F. B. LEWIS.

Existing spasmolytics are briefly reviewed, and their relation to the present series indicated. The variation of antispasmodic action with changing orientation and substitution among pyridylquinolines and related compounds is described.

By diazotising aminoquinolines and coupling the diazonium salts with pyridine, 3-, 5-, and 8-pyridylquinolines were prepared ; in the first case two (α, β) of the three possible isomerides were isolated ; only 5-α-pyridylquinoline was obtained by this route, but in the remaining case all three isomerides were obtained. In addition the 5-α-, 6-α-, 6-β-, 6-γ-, 8-α'-, and 8-β-representatives as well as 7-α-pyridylquinoline were synthesised from the appropriate aminophenylpyridine by the Skraup reaction.

INTRODUCTION.

THE following series of investigations arose out of a comprehensive study of arylpyridines and related compounds, the earlier results of which have already appeared (J., 1940, 349, 355, 358, 1279). It was anticipated that pyridylquinolines would prove of pharmacological interest, and biological examination, carried out in the laboratories of I.C.I. (Dyestuffs) Ltd., revealed that their most notable feature was a pronounced antispasmodic action with the promise of useful additions to the range of drugs suitable for treating asthmatic and other conditions.

Of existing spasmolytics, the best known are adrenaline and ephedrine and the alkaloids papaverine and atropine. Many 1-aryl- and 1-homoaryl-*iso*quinolines resembling papaverine in constitution and pharmacological action have been adopted or suggested for clinical use (*e.g.*, Ellinger, Koschara, and Seerar, *Klin. Woch.*, 1934, **13**, 411; F.P. 760,825; Slotta and Haberland, *Angew. Chem.*, 1933, **46**, 766; Bruckner and Fodor, *Ber.*, 1938, **71**, 541; Werder, *Mercks Jahresber.*, 1936, **50**, 88; B.P. 348,956; F.P. 719,638; G.P. 549,967, 613,008) and here it is particularly interesting to note that 6 : 7-methylenedioxy-1-β-pyridyl-3-methyl*iso*quinoline (G.P. 549,967) can be used in place of papaverine.

In the present studies, a wide variety of pyridylquinolines, dipyridylquinolines, and related compounds has been synthesised. As clinical trials are still in progress and as the pharmacological detail is outside the province of the present papers, only such findings as appear to be of chemical significance are given here.

Of monopyridylquinolines there was a marked dependence of activity on the relative orientation of the pyridyl and quinolyl residues. Thus the 3- and 6-pyridyl compounds were more active than the corresponding 5-, 7-, and 8-isomerides and in general the γ-pyridyl compounds were superior to either the α- or the β-derivatives, having a potency comparable with that of adrenaline. Among the lutidylquinolines the 6-isomeride was again outstanding. The dicarboxylic esters and dihydro-esters from which these bases were derived possessed only feeble antispasmodic activity. Whereas 6-lutidylquinoline was highly active, the isomeric $\alpha\alpha'$-dimethyl-6-β-pyridylquinoline was much less potent. The replacement of the pyridyl residue by amidino-, pyrryl or thiazyl groups gave disappointing results, only the last showing any promise. Among the pyridylacridines even the γ-pyridyl compounds had only very slight activity.

Schönhöfer (" Medicine in its Chemical Aspects," 1934, II, 229) has shown that the antispasmodic action of alkoxy (chiefly methoxy)-quinolines is enhanced by introducing further similar groups into *m*-positions in the quinoline ring and it was therefore of interest to observe whether a similar enhancement could be brought about in monopyridylquinolines already possessing considerable activity. This would seem to be the case, for 6 : 8-dipyridylquinoline, even as a mixture which must have contained a large proportion of α-pyridyl constituents, was at least as effective as the most active γ-monopyridylquinoline; when the pyridyl residues no longer stood in *m*-relation, as in 5 : 8-dipyridylquinoline, the activity again receded. Similarly 6-methoxy-8-pyridyl- and 8-methoxy-6-pyridyl-quinolines were superior to the simple pyridylquinoline and once again the γ-pyridyl compounds were outstanding.

PART I. MONOPYRIDYLQUINOLINES.

Prior to the present work, the preparation of two pyridylquinolines had already been recorded, but their physiological activity does not appear to have been examined. 7-β(or γ)-Pyridylquinoline (I) was prepared by the distillation of the silver salt of 5 (or 4)-7'-quinolylpyridine-3-carboxylic acid (Fischer and van Loo, *Ber.*,

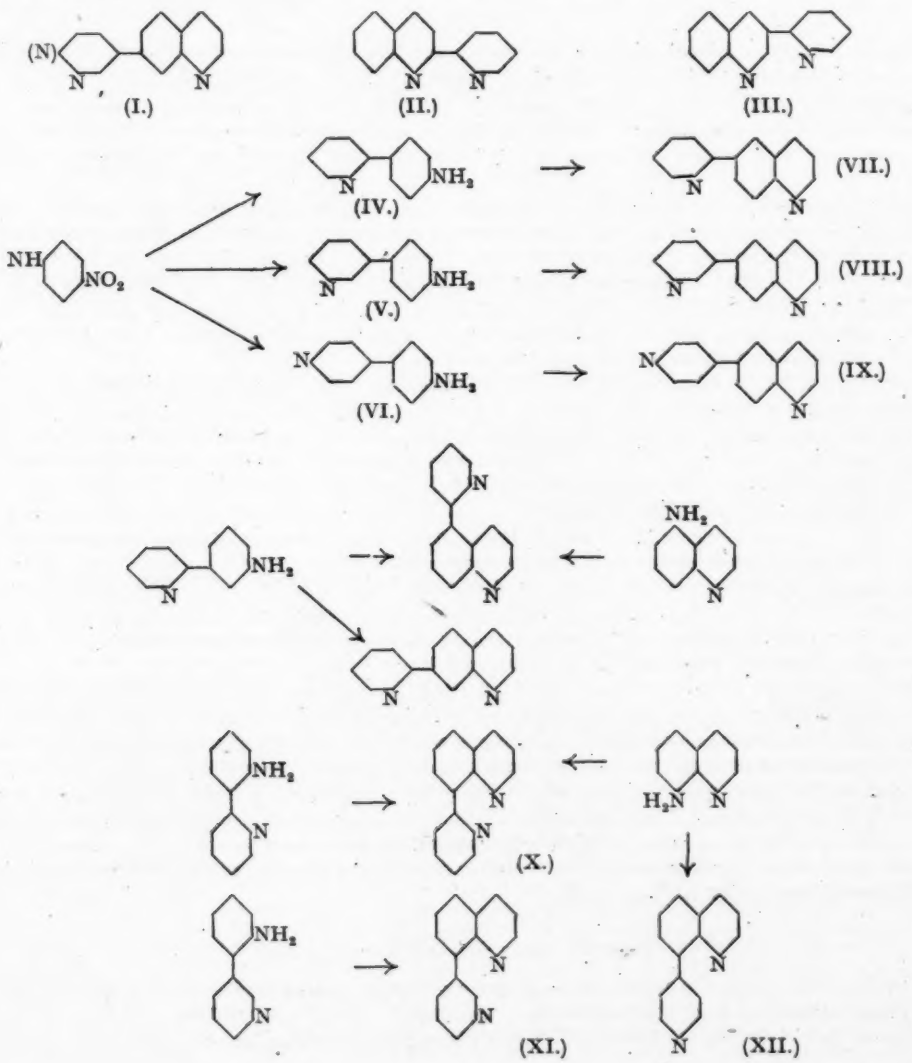
1886, **19**, 2475), and an excellent yield of 2-α-pyridylquinoline (II) was obtained by the condensation of *o*-aminobenzaldehyde with α-pyridyl methyl ketone in alcoholic potassium hydroxide (Smirnoff, *Helv. Chim. Acta*, 1921, **4**, 806).

Pyridylquinolines have now been obtained (*a*) by diazotising aminoquinolines and allowing the diazonium salts to react with pyridine; and (*b*) from the appropriate nitrophenylpyridines by reduction to the corresponding aminophenylpyridine, followed by the Skraup or Doebner–Miller reaction. Similar reactions have been embodied in B.P. 544,190 (I.C.I. Ltd., Basford and Rose).

2-Aminopyridine can be diazotised only with difficulty by the usual methods, whereas the sodium diazotate is relatively easily obtained by the interaction of the amine, amyl nitrite, and alkali. 2-Aminoquinoline has not hitherto been diazotised and it was concluded that sodium quinoline-2-diazotate offered the better likelihood of directly introducing the pyridyl residue. No difficulty was experienced in preparing the diazotate by the action of amyl nitrite and sodium ethoxide on 2-aminoquinoline, but subsequent reaction with pyridine afforded no evidence of coupling and only a small yield of 2-aminoquinoline was recovered.

4-Aminoquinoline likewise failed to give any 4-pyridylquinoline either by orthodox diazotisation in concentrated sulphuric acid and later reaction with pyridine or by the action of ethereal nitrosyl chloride on a solution of 4-aminoquinoline in excess of pyridine. In view of the abnormal and even amide nature of 2- and 4-aminoquinoline, those failures were not surprising.

3-*Pyridylquinoline.*—3-Aminoquinoline (Renshaw and Friedman, *J. Amer. Chem. Soc.*, 1939, **61**, 3321) diazotised normally and the diazonium salt reacted with pyridine to give a high yield of 3-*pyridylquinolines*. This mixture was fractionated in the form of its picrate, two pure (probably α- and β-) isomerides being isolated. That resulting in preponderating amount was regarded as 3-α-pyridylquinoline (III), the α-compound being the major constituent in all similar reactions.



5- *and* 7-*Pyridylquinoline*.—3-α-Aminophenylpyridine (Heilbron, Hey, and Lambert, J., 1940, 1281) was converted by means of the Skraup reaction into a mixture of 5-α- and 7-α-*pyridylquinoline*; separation by fractional crystallisation from light petroleum gave the pure components, the separate identities of which were proved by the following unambiguous method. Diazotisation of 5-aminoquinoline and reaction with pyridine in the normal way gave a mixture of 5-pyridylquinolines, from which 5-α-pyridylquinoline was isolated by fractionally crystallising the picrates from acetone.

6-*Pyridylquinolines*.—α-, β-, and γ-4-Nitrophenylpyridine, isolated from the reaction between diazotised *p*-nitroaniline and pyridine (Haworth, Heilbron, and Hey, J., 1940, 349), were separately reduced to the corresponding α- (IV), β-(V), and γ-4-aminophenylpyridine (VI) (Heilbron, Hey, and Lambert, J., 1940, 1279), which were converted, as indicated above, into the corresponding 6-α-(VII), 6-β-(VIII), and 6-γ-*pyridylquinoline* (IX).

8-*Pyridylquinolines*.—8-Nitroquinoline was reduced to 8-aminoquinoline; this base was dizaotised and on reacting with pyridine gave a mixture of 8-pyridylquinolines from which three pure compounds were isolated by fractionally crystallising the picrate mixture. One of these was identified as 8-α-pyridylquinoline (X), for it was also obtained by the Skraup reaction on α-2-aminophenylpyridine. β-2-Nitrophenylpyridine gave an *amine* on reduction which afforded 8-β-*pyridylquinoline* (XI) identical with another of the above products, and the structure of 8-γ-*pyridylquinoline* (XII) followed by elimination.

Experimental.

3-*Pyridylquinoline*.—A solution of 3-aminoquinoline (37 g.) (Renshaw and Friedman, *loc. cit.*) in water (50 c.c.) and concentrated hydrochloric acid (100 c.c.) was cooled to 5°, sodium nitrite (18 g.) in water (50 c.c.) added as quickly as possible below 10°, and the solid diazonium salt dissolved by addition of ice and water (800 g.). The solution was introduced during 2 hours into pyridine (1 l.), which was stirred and maintained at 50°. The reaction solution was made alkaline with ammonia, and pyridine removed in steam. The residual tar was extracted with boiling benzene, and the extract distilled, eventually in a vacuum. The 3-pyridylquinolines were collected at 165—185°/0·2 mm. as a golden-yellow oil (25 g.) which soon solidified. After a single crystallisation from benzene–light petroleum the mixture of isomerides had m. p. 70—80° (Found : N, 14·0. $C_{14}H_{10}N_2$ requires N, 13·6%).

When the picrates were crystallised from *cyclo*hexanone, the *α-isomeride* was readily obtained pure; it had m. p. 227—229° (Found : N, 16·3. $C_{14}H_{10}N_2,C_6H_3O_7N_3$ requires N, 16·1%). 3-α-*Pyridylquinoline*, liberated by warming the picrate with 10% sodium hydroxide solution, crystallised from benzene–light petroleum in hard white needles, m. p. 101·5° (Found : N, 13·4%). The residual picrate was crystallised from acetone to yield a second *isomeride*, m. p. 196° (decomp.) (Found : N, 16·2%). The free *base*, liberated as in the preceding preparation, separated in white needles, m. p. 123°, from benzene–light petroleum (Found : N, 13·8%).

5- *and* 7-α-*Pyridylquinoline*.—α-3-Aminophenylpyridine (10 g.), anhydrous glycerol (13·5 g.), 98% sulphuric acid (9 c.c.), and anhydrous arsenic acid (8·5 g.) were heated together at 160° for 6 hours. After dilution with water, the solution was made alkaline and extracted with benzene. Distillation of the residue after removal of solvent gave a brown oil (3·7 g.), b. p. 140—155°/0·4 mm., which solidified on standing. Several crystallisations from light petroleum yielded 7-α-*pyridylquinoline* in clusters of needles, m. p. 87—88° (Found : C, 81·9; H, 4·9. $C_{14}H_{10}N_2$ requires C, 81·6; H, 4·9%); the picrate had m. p. 221°. The mother-liquors from the 7-compound gave 5-α-*pyridylquinoline*, which separated from light petroleum in fine colourless needles, m. p. 88—89° (Found : C, 81·8; H, 5·0%). The picrate had m. p. 212°. 5-Nitroquinoline, separated from the mixture of 5- and 8-nitroquinoline obtained by direct nitration of quinoline (Le Fèvre and Le Fèvre, J., 1935, 1472), was reduced with tin and hydrochloric acid to 5-aminoquinoline (Dikshoorn, *Rec. Trav. chim.*, 1929, **48**, 147). To a solution of this base (11 g.) in concentrated hydrochloric acid (64 c.c.) at 90°, water (41 c.c.) was added, and the whole cooled quickly to 0°. The paste of hydrochloride was diazotised at 0° with 5N-sodium nitrite (14 c.c.), and the diazo-solution stirred, during 1 hour, into pyridine (200 c.c.) at 50—60°. After a further hour's stirring at 70—80°, excess of a concentrated solution of caustic soda was added, the pyridine layer separated, and the excess of pyridine removed with steam. The tarry non-volatile layer was extracted with benzene, and the extracts distilled. After removal of solvent 5-pyridylquinolines (4·5 g.) were collected at 152—172°/<0·1 mm. as a red-brown oil. This mixture was treated with alcoholic picric acid, and the mixed picrates fractionally crystallised from acetone. 5-α-Pyridylquinoline picrate separated in fine yellow needles, m. p. 212°, not depressed by the picrate of the base of m. p. 88—89° (above).

6-*Pyridylquinolines*.—α-4-Aminophenylpyridine (Heilbron, Hey, and Lambert, J., 1940, 1279) (5 g.) was heated with anhydrous glycerol (9 g.), concentrated sulphuric acid (8·5 g.), and anhydrous arsenic acid (4·0 g.) at 160—170° for 6 hours. The mixture was cooled, diluted with 2 vols. of water, kept overnight, and filtered; the filtrate was made just alkaline with dilute caustic soda solution, and the precipitated oily solid extracted with benzene. After removal of benzene, distillation at 70—150° in a high vacuum gave 6-α-*pyridylquinoline* as a pale green solid, which crystallised from light petroleum (b. p. 40—60°) in small colourless needles, m. p. 82—83° (Found : C, 81·6; H, 4·6%). β-4-Aminophenylpyridine (Heilbron, Hey, and Lambert, *loc. cit.*) (10 g.) was treated as described for the corresponding α-isomeride, and the precipitated oil extracted with benzene. After removal of benzene, distillation at 170—173°/0·1 mm. gave a yellow viscous liquid (7·7 g.) which did not solidify. This product was treated with alcoholic picric acid (2 mols.); the *dipicrate* crystallised from glacial acetic acid in small needles, m. p. 249—250° (Found : N, 16·7. $C_{14}H_{10}N_2,2C_6H_3O_7N_3$ requires N, 16·9%). Heating with 20% caustic soda solution gave a viscous liquid which crystallised slowly. Recrystallisation from light petroleum yielded colourless hygroscopic needles of 6-β-*pyridylquinoline*, m. p. 32—34° (Found : C, 81·3; H, 4·7%). γ-4-Aminophenylpyridine (Heilbron, Hey, and Lambert, *loc. cit.*) (1·5 g.), sodium *m*-nitrobenzenesulphonate (2·5 g.), and glycerol in sulphuric acid (66%; 13 g.) were refluxed for 5 hours. The mixture was cooled, diluted with water to 50 c.c., filtered, and made alkaline. After 12 hours, the precipitated base was extracted with benzene. Distillation of the residue, obtained on removal of solvent, at 90—110° in a high vacuum gave 6-γ-*pyridylquinoline* (1·5 g.), which separated from light petroleum in small prisms, m. p. 104—105° (Found : C, 82·0; H, 4·7%).

8-*Pyridylquinolines*.—8-Nitroquinoline (Meigen, *J. pr. Chem.*, 1908, **77**, 473) (83 g.) in ethanol (147 c.c.), water (24 c.c.), and concentrated hydrochloric acid (9·6 c.c.) was treated with iron filings (143 g.), and the whole stirred under reflux on the steam-bath for 24 hours. After being made alkaline, the liquid was filtered, the sludge extracted with ethanol, and the combined extracts and filtrate evaporated to dryness. Crystallisation of the residue from benzene–light petroleum yielded 8-aminoquinoline (47 g.) in small plates, m. p. 64°. The amine (47 g.), dissolved in concentrated hydrochloric acid (470 c.c.) and water (180 c.c.), was diazotised at 0° with sodium nitrite (18 g.) in water (60 c.c.), and the filtered diazonium solution added with stirring during 1½ hours to pyridine (400 c.c.) at 60°. After a further hour's stirring at

60°, a concentrated solution of caustic soda was added, and the pyridine layer separated. The excess of pyridine was removed in steam, and the tarry residue extracted with benzene. After removal of solvent, distillation at 120° in a high vacuum gave a viscous liquid (10·2 g.). After chromatography from benzene on alumina the material recovered from the filtrate was converted into a mixture of picrates, which on fractional crystallisation from acetone afforded 8-α-*pyridylquinoline picrate* in fine needles, m. p. 209—210° (Found : N, 16·0. $C_{14}H_{10}N_2,C_6H_3O_7N_3$ requires N, 16·1%); the free base was identical with 8-α-pyridylquinoline obtained by the Skraup reaction (see below); the *styphnate* separated from methyl ethyl ketone in yellow needles, m. p. 181·5—182·5° (decomp.) (Found : N, 15·5. $C_{14}H_{10}N_2,C_6H_3O_8N_3$ requires N, 15·5%). Further crystallisation gave 8-β-pyridylquinoline picrate, m. p. 224—225°, both the picrate and the free base being identified with the product of the Skraup reaction (see below). Elution of the alumina with ethanol and crystallisation of the eluate as picrate from the same solvent gave 8-γ-*pyridylquinoline picrate* in yellow needles, m. p. 238—240° (decomp.) (Found : N, 15·8%); the free *base* separated from benzene–light petroleum in colourless prisms, m. p. 127° (Found : C, 81·6; H, 4·9%).

α-2-Aminophenylpyridine (4·1 g.), sodium *m*-nitrobenzenesulphonate (8·2 g.), glycerol (10 g.), sulphuric acid (*d* 1·56, 50 c.c.), and vanadium pentoxide (0·1 g.) were refluxed for 5½ hours. After cooling, the mixture was diluted with ice and water, heated to 80°, filtered, and the filtrate made alkaline with ammonia. The solution was cooled at 0° for several hours, the supernatant liquid decanted, and the resultant black tar extracted thoroughly with benzene. The extract was filtered through a short column of alumina, the clear filtrate giving crude 8-α-*pyridylquinoline* (2 g.) on evaporation. Recrystallised from benzene–light petroleum, it gave large prisms, m. p. 74—76°, identical with the product obtained as picrate above (Found : N, 13·5. $C_{14}H_{10}N_2$ requires N, 13·6%). β-2-Nitrophenylpyridine (Haworth, Heilbron, and Hey, J., 1940, 354) (9·5 g.) in ethanol (95 c.c.) was reduced with stannous chloride (51 g.) and concentrated hydrochloric acid. After removal of most of the ethanol, a large excess of concentrated caustic soda solution was added, and the base extracted with ether. Distillation of the residue, obtained on removal of the ether, at 168°/0·06 mm. gave β-2-aminophenylpyridine (4·9 g.) as a viscous liquid, which solidified on cooling to a snow-white mass of needles, m. p. 72°. β-2-Aminophenylpyridine (3·6 g.) was heated with anhydrous glycerol (4·8 g.), anhydrous arsenic acid (3·2 g.), and concentrated sulphuric acid (3·2 c.c.) at 160—170° for 7 hours. The mixture was cooled, diluted with water (2 vols.), and made alkaline. After standing overnight, the tarry precipitate was extracted with benzene. Distillation of the residue, after removal the solvent, at 120° in a high vacuum gave 8-β-*pyridylquinoline*, which separated from benzene–light petroleum in colourless needles, m. p. 111—112° (Found : C, 82·0; H, 5·0%). The *picrate* separated from acetone in very fine needles, m. p. 226° (Found : N, 16·0. $C_{14}H_{10}N_2,C_6H_3O_7N_3$ requires N, 16·1%).

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107. *New Therapeutic Agents of the Quinoline Series. Part II. Dipyridylquinolines.*

By A. H. COOK, I. M. HEILBRON, D. H. HEY, A. LAMBERT, and (in part) A. SPINKS.

α-4-Aminophenylpyridine has been converted into 8-nitro-6-α-pyridylquinoline and thence into 6-α-pyridyl-8-pyridylquinoline. 6 : 8-Dipyridylquinoline has also been prepared by stepwise introduction of pyridyl groups to yield 1 : 3-dipyridylbenzene, introduction into this of an amino-group, and submission of the product to the Skraup reaction. Similarly, pyridyl groups were introduced stepwise in 1 : 4-positions into the benzene nucleus, and the resulting dipyridylbenzene eventually converted into 5 : 8-dipyridylbenzene.

THE compounds described below represent attempts to increase the spasmolytic activity of pyridylquinolines by the introduction of a second pyridyl group.

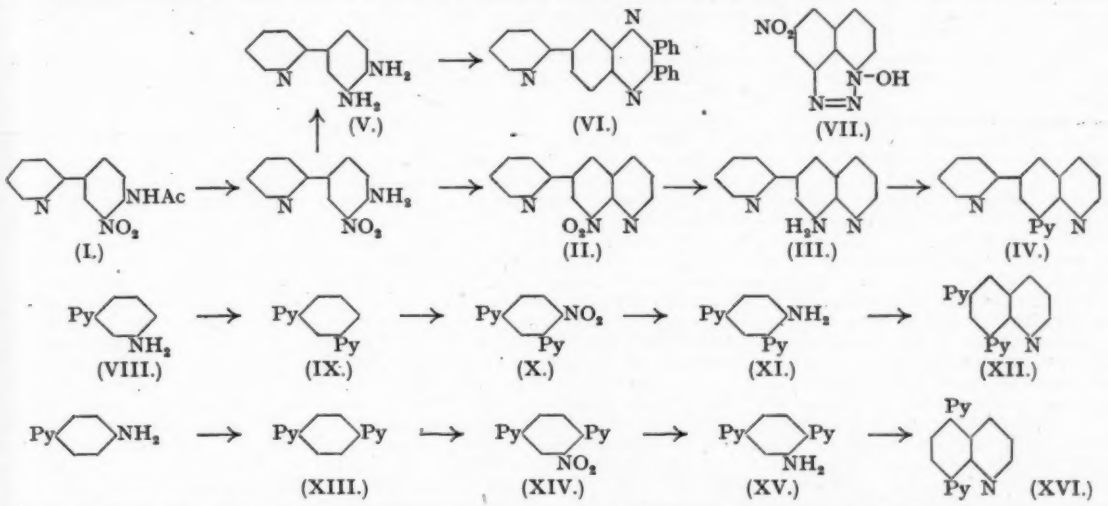
On nitration α-4-acetamidophenylpyridine (Heilbron, Hey, and Lambert, J., 1940, 1281) gave α-3-*nitro*-4-*acetamidophenylpyridine* (I), which was hydrolysed to α-3-*nitro*-4-*aminophenylpyridine*. The application of the Skraup reaction to the latter gave 8-*nitro*-6-α-*pyridylquinoline* (II), which was reduced to 8-*amino*-6-α-*pyridylquinoline* (III). By diazotisation of this amine and subsequent reaction with pyridine, a mixture of 6-α-*pyridyl*-8-α (β and γ)-*pyridylquinoline* (IV) was obtained. The constitution of α-3-nitro-4-aminophenylpyridine was confirmed by its reduction to α-3 : 4-*diaminophenylpyridine* (V) and conversion of this into 2 : 3-*diphenyl*-6-α-*pyridylquinoxaline* (VI).

Alternative methods for the preparation of dipyridylquinolines were then investigated. No success attended attempts to tetrazotise 6 : 8-diaminoquinoline, so the direct simultaneous introduction of two pyridyl groups appeared impracticable. 6-Nitro-8-aminoquinoline reacted with nitrous acid; the product, however, was not a diazonium salt but resembled those obtained from other diazotised 8-aminoquinolines when deficiency of acid is used (D.R.-P. 576,119). It is provisionally regarded as the cyclised triazen (VII).

Mixed 3-nitrophenylpyridines, prepared by the reaction between diazotised *m*-nitroaniline and pyridine (Haworth, Heilbron, and Hey, J., 1940, 349), were reduced to the corresponding amino-compounds (VIII) (cf. Heilbron, Hey, and Lambert, *loc. cit.*), which on diazotisation and subsequent reaction with pyridine gave a mixture of 1 : 3-*dipyridylbenzenes* (IX) in 50% yield. The latter was very resistant to nitration, but a single nitro-group was finally introduced by heating the mixed *dinitrates* with concentrated sulphuric acid. The product, regarded as a mixture of 4-*nitro*-1 : 3-*dipyridylbenzenes* (X) (compare the nitration of *m*-terphenyl; France, Heilbron, and Hey, J., 1939, 1288), was reduced to a mixture of the corresponding amines (XI), which was converted into a mixture of 6 : 8-*dipyridylquinolines* (XII) by means of the Skraup reaction. This mixture had a higher melting point than that of 6-α-pyridyl-8-α(β and γ)-pyridylquinolines and the difference is attributed to the presence of a greater proportion of higher-melting isomerides.

p-Nitroaniline was converted into *p*-nitrophenylpyridines and thence by reduction into a mixture of *p*-aminophenylpyridines. Diazotisation of this mixture and reaction of the aqueous diazonium salt with pyridine gave a considerable yield of p-*dipyridylbenzene* (XIII). The material so obtained probably consists of six isomerides,

the separation and identification of which have not been attempted. Since the final quinoline was required only for comparative physiological tests, the dipyridylbenzene was converted into its nitrate mixture and thence into a *mononitrodipyridylbenzene* (XIV) mixture by heating with sulphuric acid. Each of the unsymmetrical *p*-dipyridylbenzenes may yield two mononitro-derivatives and the total number of nitro-compounds in the mononitration product may be as high as nine; it was not surprising, then, that the nitrodipyridyl-



benzene mixture was an oil. It was converted into 2 : 5-*dipyridylaniline* (XV), a yellow glass, in the usual manner and this into 5 : 8-*dipyridylquinoline* (XVI) by a Skraup reaction using dilute sulphuric acid in presence of vanadium pentoxide (cf. B.P. 394,416). A product of high quality was obtained in good yield; again nine isomerides are theoretically possible, but the quinoline readily solidified and repeated crystallisation afforded a substance of sharp melting point which was probably a single isomeride.

Experimental.

α-3-*Nitro*-4-*acetamidophenylpyridine*.—α-4-Acetamidophenylpyridine (49 g.) (Heilbron, Hey, and Lambert, J., 1940, 1282) was stirred in small portions into nitric acid (*d* 1·5; 200 c.c.) at 0°; after ½ hour, the solution was poured on ice, and the excess of acid neutralised with caustic soda solution. Crystallisation of the pale yellow precipitate from alcohol gave α-3-*nitro*-4-*acetamidophenylpyridine* (45 g.) in silky needles, m. p. 142—143° (Found: C, 60·8; H, 4·6. $C_{13}H_{11}O_3N_3$ requires C, 60·7; H, 4·3%).

The preceding compound (45 g.) was refluxed with a solution of caustic soda (60 g.) in water (300 c.c.) for 20 minutes. Crystallisation of the resulting solid from benzene gave α-3-*nitro*-4-*aminophenylpyridine* in red needles, m. p. 148—149° (Found: C, 61·5; H, 4·2. $C_{11}H_9O_2N_3$ requires C, 61·4; H, 4·2%).

8-*Nitro*-6-α-*pyridylquinoline*.—This was prepared from α-3-nitro-4-aminophenylpyridine (17 g.) as described under 6-α-pyridylquinoline (preceding paper). After removal of solvents the residue was crystallised from alcohol (charcoal), giving 8-*nitro*-6-α-*pyridylquinoline* (6·3 g.) in pale yellow needles, m. p. 123—124° (Found: C, 66·8; H, 3·6. $C_{14}H_9O_2N_3$ requires C, 66·9; H, 3·6%).

8-*Amino*-6-α-*pyridylquinoline*.—A solution of 8-nitro-6-α-pyridylquinoline (9 g.) in alcohol (160 c.c.), water (2 c.c.), and hydrochloric acid (0·7 c.c.) was stirred with iron filings (11 g.) under reflux on the steam-bath for 24 hours. After being made alkaline with caustic soda solution, the liquid was filtered, the sludge extracted with alcohol, and the combined extracts and filtrate evaporated to dryness. Crystallisation of the residue from benzene (charcoal) gave 8-*amino*-6-α-*pyridylquinoline* (6·7 g.) in reddish-yellow plates, m. p. 125—126° (Found: C, 75·9; H, 5·3. $C_{14}H_{11}N_3$ requires C, 76·0; H, 5·0%).

6-α-*Pyridyl*-8-α(β and γ)-*pyridylquinoline*.—8-Amino-6-α-pyridylquinoline (3 g.), dissolved in concentrated hydrochloric acid (15 c.c.) and water (5 c.c.), was diazotised at 5—10° with sodium nitrite (0·96 g.) in water. After 10 minutes, the liquid was filtered and stirred into pyridine (100 c.c.) at 45—50°. Stirring was continued for 2 hours at 50°, excess of a concentrated solution of caustic soda then added, the pyridine layer separated, and excess of pyridine removed in steam. When cool, the aqueous layer was decanted, and the tarry residue extracted with benzene. After removal of the benzene, distillation at 90—130° in a high vacuum gave a pale yellow, viscous oil which formed a hard glass on cooling. Crystallisation from benzene–light petroleum (b. p. 40—60°) yielded 6-α-*pyridyl*-8-α(β and γ)-*pyridylquinoline* (0·9 g.) in small colourless needles, m. p. 118—121° (Found: C, 80·8; H, 4·4. $C_{19}H_{13}N_3$ requires C, 80·6; H, 4·6%).

α-3 : 4-*Diaminophenylpyridine*.—α-3-Nitro-4-aminophenylpyridine (0·8 g.) in alcohol (100 c.c.) was reduced with stannous chloride (5 g.) and concentrated hydrochloric acid (6 c.c.) in the normal manner. After the addition of a large excess of concentrated caustic soda solution, the base was extracted in ether and crystallised from benzene–light petroleum (b. p. 60—80°), α-3 : 4-*diaminophenylpyridine* being obtained in almost colourless needles, m. p. 126—126·5° (Found: C, 71·4; H, 6·0. $C_{11}H_{11}N_3$ requires C, 71·3; H, 5·9%). A solution of α-3 : 4-diaminophenylpyridine (0·1 g.) and benzil (0·13 g.) in alcohol was refluxed for ½ hour. 2 : 3-*Diphenyl*-6-α-*pyridylquinoxaline* separated on cooling in pale yellow prisms, m. p. 198—199° (Found: C, 83·7; H, 4·8. $C_{23}H_{17}N_3$ requires C, 83·5; H, 4·7%).

Reaction of Diazotised 3-*Aminophenylpyridine with Pyridine*.—A mixture of 3-nitrophenylpyridines prepared as described by Haworth, Heilbron, and Hey (J., 1940, 349) was reduced with stannous chloride and hydrochloric acid. The resulting amino-compounds distilled at 176—181°/1 mm. as a colourless oil which partially solidified on cooling. The solid material crystallised from moist alcohol in plates, m. p. 102—104°. This corresponds to the monohydrate of α-3-aminophenylpyridine described by Forsyth and Pyman (J., 1926, 2912). The mixture of bases was diazotised, and the red diazonium solution added with stirring during 1½ hours to excess of pyridine at 20—22°. After standing

overnight, the mixture was rendered alkaline with 30% aqueous caustic soda, the pyridine layer removed, and the excess of pyridine distilled in steam. The residue was extracted with benzene and after the removal of the solvent, distillation at 195—218°/1 mm. gave a mixture of 1 : 3-dipyridylbenzenes as a yellow oil in 50% yield. The *dinitrate*, crystallised from alcohol, had m. p. 110—120° (Found : C, 53·6; H, 4·1. $C_{16}H_{12}N_2,2HNO_3$ requires C, 53·6; H, 3·9%).

4-Nitro-1 : 3-dipyridylbenzenes.—Mixed 1 : 3-dipyridylbenzene dinitrates (14 g.) were dissolved in concentrated sulphuric acid and heated on the steam-bath for 1 hour. The solution was then cooled, diluted with water, and made alkaline with caustic soda solution. A mixture of *4-nitro-1 : 3-dipyridylbenzenes* was obtained as a pale yellow oil (10·5 g.), which crystallised from dilute alcohol in almost colourless needles, m. p. 137—140° (Found : C, 69·1; H, 4·2. $C_{16}H_{11}O_2N_3$ requires C, 69·3; H, 4·0%).

The mixture of 4-nitro-1 : 3-dipyridylbenzenes (10 g.) in alcohol (100 c.c.) was reduced with stannous chloride (60 g.) and concentrated hydrochloric acid (60 c.c.), excess of a concentrated solution of caustic soda added, and the liberated base extracted with benzene. After removal of the benene, distillation at 210—225°/0·004 mm. gave a mixture of 4-amino-1 : 3-dipyridylbenzenes (7·5 g.) as a pale yellow oil, which formed a hard glass on cooling.

6 : 8-Dipyridylquinolines.—A solution of mixed 4-amino-1 : 3-dipyridylbenzenes (7 g.), sodium *m*-nitrobenzenesulphonate (14 g.), and glycerol (15 g.) in sulphuric acid (66%, 80 c.c.) was refluxed with stirring for 6 hours, cooled, diluted with water to 400 c.c., and made alkaline with caustic soda solution. The material extracted after 12 hours from the tarry precipitate with benzene was crystallised from benzene–light petroleum (b. p. 60—80°), giving a mixture of *6 : 8-dipyridylquinolines* (3·2 g.) in needles, m. p. 152—156° (Found : C, 80·9; H, 4·6. $C_{19}H_{13}N_3$ requires C, 80·6; H, 4·6%).

p-Dipyridylbenzene.—*p*-Aminophenylpyridine (b. p. 160—180°/0·5 mm., 62·5 g.) in 5N-hydrochloric acid (300 c.c.) was diazotised with sodium nitrite (26 g. in 50 c.c. of water), and the solution cooled and added during 30 mins. to pyridine (800 c.c.) at −10°; the temperature rose to about 40°. The dark solution was stirred overnight at room temperature, sodium hydroxide (200 g.) added, and the pyridine removed in steam. The residue was extracted repeatedly with benzene. Removal of solvent, followed by distillation, gave dipyridylbenzene (b. p. 210—230°/0·002 mm., 36 g.) as a yellow oil which rapidly solidified. Solution in ethanol, followed by cautious addition of concentrated nitric acid, gave the insoluble mixed nitrates. The nitrate mixture in concentrated sulphuric acid (65 c.c.) was heated on the steam-bath for 90 minutes, cooled, and poured on ice. Ammonia was added, the separated oil extracted with benzene, and the combined extracts boiled with charcoal. Removal of solvent gave a brown oil which could not be crystallised. Preparation of the nitrate and three crystallisations of the latter from 2N-nitric acid gave a product which, although crystalline, gave an oily base on regeneration. Repeated nitration effected no improvement and the free base was therefore converted directly into the corresponding amine. 2 : 5-Dipyridylnitrobenzene (25 g.) was treated in ethanol (300 c.c.) with stannous chloride (200 g.) in concentrated hydrochloric acid (200 c.c.), and the solution heated on the steam-bath overnight. After removal of ethanol, the residue was treated rapidly with 30% sodium hydroxide solution (1200 c.c.), and the clear aqueous layer extracted with benzene. Removal of benzene, followed by distillation, gave 2 : 5-dipyridylaniline (b. p. 210—230°/0·1 mm.) as a yellow glass (14·5 g.). This base (13 g.), sulphuric acid (60%, 180 c.c.), glycerol (28 g.), arsenic acid (36 g.), and vanadium pentoxide (0·55 g.) were refluxed for 6 hours at 160—170°. The solution was cooled, diluted with water, filtered after a few hours, and made alkaline with sodium hydroxide. After 24 hours the precipitate was collected and extracted with boiling benzene; the combined extracts were refluxed with charcoal, filtered, and evaporated to *ca.* 50 c.c. The product after filtration and drying was a white powder (9 g.), m. p. 140—154°. Two crystallisations from benzene–light petroleum (b. p. 80—100°) gave a fraction (3·5 g.) crystallising in colourless needles, m. p. 157—163°. Further crystallisation of a portion of this fraction gave long colourless needles, m. p. 167° (Found : C, 80·8; H, 4·5. $C_{19}H_{13}N_3$ requires C, 80·6; H, 4·6%). From the mother-liquors concentration gave a fraction (4·5 g.), m. p. 138—149°, crystallising in micro-needles (Found : C, 80·8; H, 4·8%).

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108. *New Therapeutic Agents of the Quinoline Series. Part III. Methoxy-, Hydroxy-, and Alkyl-pyridylquinolines.*

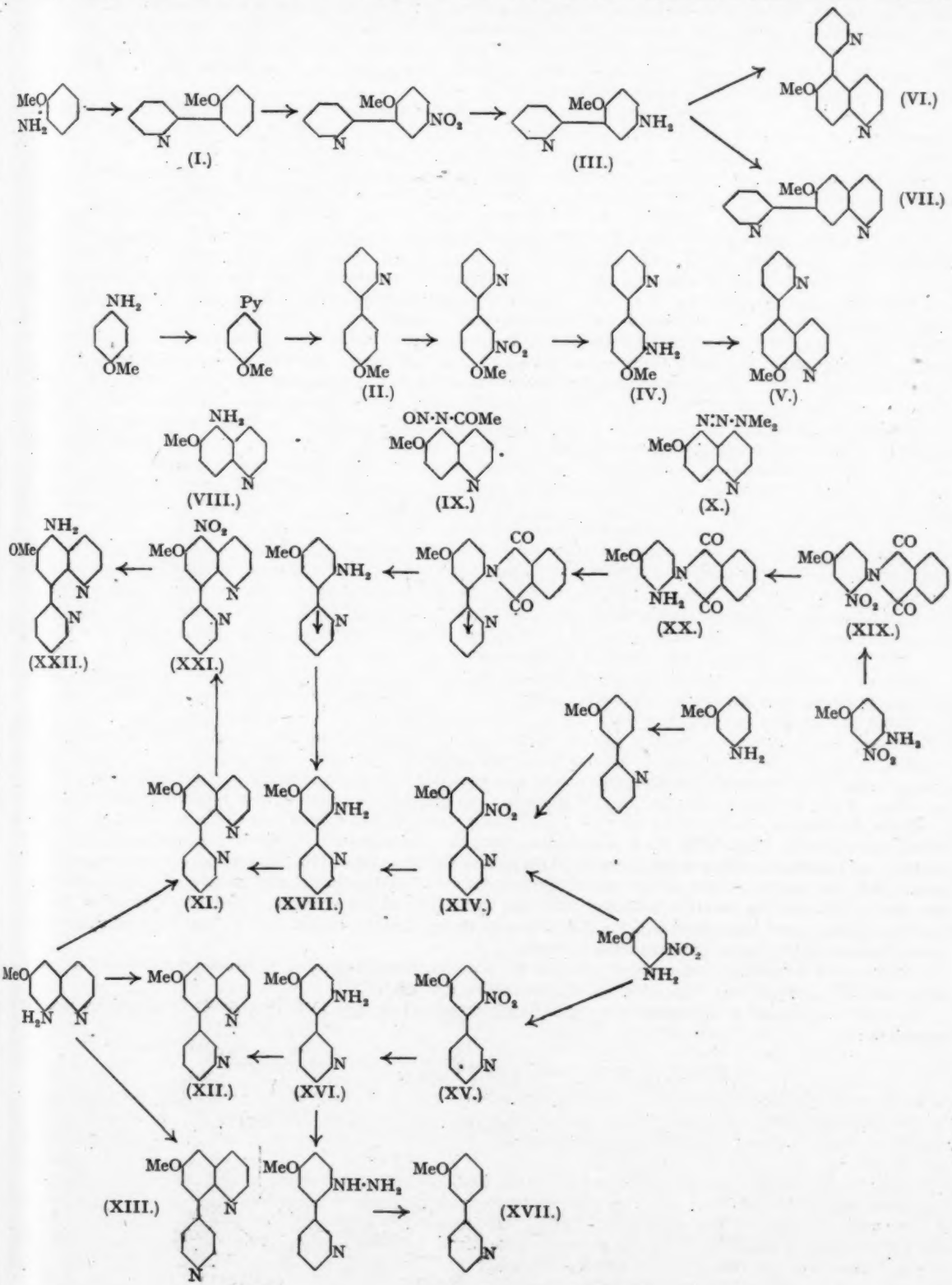
By H. COATES, A. H. COOK, I. M. HEILBRON, D. H. HEY, A. LAMBERT and (in part) F. B. LEWIS.

A representative series of methoxypyridylquinolines has been prepared by submitting pyridylanisidines of proved orientation to the Skraup reaction, as well as by directly introducing the pyridyl group into the quinoline system. A hydroxypyridylquinoline was similarly synthesised. By means of the Doebner–Miller reaction several aminophenylpyridines were converted into pyridylquinaldines, and a higher alkyl (*tert.*-butyl) pyridylquinoline was also synthesised. Preparations of pyridylacetoacetanilides and attempts to cyclise them to quinoline derivatives are also described.

As alkoxyl groups are a feature of most spasmolytic *iso*quinolines, the preparation and examination of representative methoxypyridylquinolines was desirable.

Both α-2- (I) and α-4-methoxyphenylpyridine (II) isolated from the reaction between the appropriate diazotised anisidine and pyridine (Haworth, Heilbron, and Hey, J., 1940, 358) have been separately nitrated (*loc. cit.*) and reduced to *α-3-amino-6-methoxyphenylpyridine* (III) and *α-3-amino-4-methoxyphenylpyridine* (IV) respectively. Each of these amino-compounds was converted into the quinoline by means of the Skraup reaction. The latter amine gave *8-methoxy-5-α-pyridylquinoline* (V) exclusively. From the former, *6-methoxy-5-* and *-7-α-pyridylquinoline* (VI) and (VII) were isolated by fractional crystallisation of the mixed picrates from acetone. With a view to proving the separate identities of these two isomerides, an attempt was made to synthesise 6-methoxy-5-α-pyridylquinoline by the following unambiguous method. 6-Methoxyquinoline, prepared from *p*-anisidine by Skraup's method, was nitrated as described by Jacobs and Heidelberger (*J. Amer. Chem. Soc.*, 1920, **42**, 2285; cf. Decker and Engler, *Ber.*, 1909, **42**, 1740), and the constitution of the resulting 5-nitro-6-methoxyquinoline proved by demethylation to the known 5-nitro-6-hydroxyquinoline. Reduction with iron filings and a dilute solution of hydrochloric acid in alcohol then gave 5-amino-6-methoxyquinoline (VIII). The use of stannous chloride and hydrochloric acid for this reduction (cf. Jacobs and Heidelberger, *loc. cit.*) gave a product containing chlorine. Although it has been established by Heilbron, Hey, and their

collaborators (J., 1940, 349, 355, 358, 1279) that in general a mixture of α-, β-, and γ-arylpyridines is obtained when an aqueous solution of a diazotised arylamine is added to excess of pyridine, the reaction of diazotised

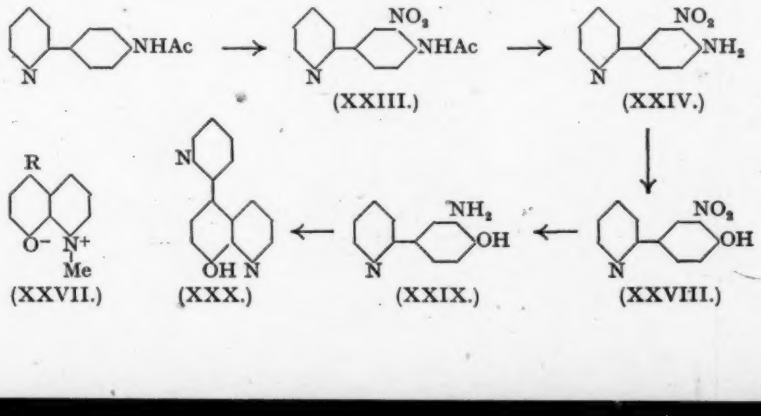


5-amino-6-methoxyquinoline with pyridine gave a solid tarry product, soluble in both acid and alkali, from which none of the required pyridylmethoxyquinoline could be isolated. A similar product also resulted from the action of the zinc chloride stabilised diazonium salt on pyridine (cf. Hodgson and Marsden, J., 1940, 208). Further attempts to effect the union of the quinoline and pyridine nuclei were made through the nitrosoacetamido-derivative (IX) (cf. Haworth, Heilbron, and Hey, J., 1940, 372) and also through the *triazen* (X) obtained by the action of the diazotised 5-amino-6-methoxyquinoline on dimethylamine (cf. B.P. 513,846), but none of the required product was obtained in either case.

From the reaction between aqueous diazotised 8-amino-6-methoxyquinoline and pyridine a mixture of isomerides has been obtained from which 6-*methoxy*-8-α- (XI), 6-*methoxy*-8-β- (XII) and 6-*methoxy*-8-γ-*pyridylquinoline* (XIII) were isolated by fractional crystallisation of the mixed *picrates* from acetone. With a view to placing the constitutions of these compounds beyond doubt, the possibility of synthesising them from the three isomeric 3-methoxyphenylpyridines by successive nitration, reduction and application of the Skraup reaction was investigated. Nitration of α-3-methoxyphenylpyridine (Haworth, Heilbron, and Hey, J., 1940, 358) gave a liquid product fom which two *mononitro*-compounds of unknown constitution, as well as α-2-*nitro*-5-*methoxyphenylpyridine* (XIV), were isolated in the form of *picrates*, but the low yield of these compounds rendered this method of synthesis impracticable. A second synthetic route was therefore examined and 6-methoxy-8-α-pyridylquinoline (XI) and 6-methoxy-8-β-pyridylquinoline (XII) were finally obtained by unambiguous methods. A mixture of 4- and 6-nitro-*m*-acetanisidide, prepared by the nitration of *m*-acetanisidide, was separated into its components as described by Reverdin and Widmer (*Ber.*, 1913, **46**, 4071) and hydrolysed. Addition of aqueous diazotised 4-nitro-*m*-anisidine to pyridine gave a mixture of 2-nitro-5-methoxyphenylpyridines in 22% yield. This comparatively low yield was due to the simultaneous formation of a considerable quantity of *p*-nitroanisole by elimination of the amino-group. From this mixture, α- (XIV) and β-2-amino-5-methoxyphenylpyridine (XV) were isolated by fractional crystallisation of the mixed picrates, but, although γ-2-nitro-5-methoxyphenylpyridine was probably present in small quantity, it was not found possible to isolate it owing to lack of material. The identity of α-2-nitro-5-methoxyphenylpyridine picrate with the corresponding compound isolated from the product obtained by the direct nitration of α-3-methoxyphenylpyridine placed the constitution of the compound beyond doubt. The constitution of β-2-nitro-5-methoxyphenylpyridine was proved by reduction to β-2-*amino*-5-*methoxyphenylpyridine* (XVI), followed by diazotisation, reduction to the hydrazine, and treatment with copper acetate to give β-3-*methoxyphenylpyridine* (XVII), the constitution of which was established by elimination following the synthesis of γ-3-methoxyphenylpyridine by an unambiguous method. Thus γ-3-nitrophenylpyridine, isolated from the product of the reaction between aqueous diazotised *m*-nitroaniline and pyridine (Haworth, Heilbron, and Hey, J., 1940, 1279), was converted into γ-3-*hydroxyphenylpyridine* through the diazonium salt. Treatment with diazomethane then gave γ-3-methoxyphenylpyridine, the picrate of which was identical with the compound of similar m. p. obtained by Haworth, Heilbron, and Hey (J., 1940, 361) from the product of the reaction between diazotised *m*-anisidine and pyridine. Reduction of α-2-nitro-5-methoxyphenylpyridine gave α-2-amino-5-methoxyphenylpyridine (XVIII), which was converted into 6-methoxy-8-α-pyridylquinoline (XI) by means of the Skraup reaction. In similar manner β-2-amino-5-methoxyphenylpyridine yielded 6-methoxy-8-β-pyridylquinoline (XII). Both these quinoline derivatives were shown to be identical with the corresponding compounds obtained by the reaction between aqueous diazotised 8-amino-6-methoxyquinoline and pyridine and the constitution of 6-methoxy-8-γ-pyridylquinoline (XIII) is thus established by elimination. An alternative route to the 2-amino-5-methoxyphenylpyridines, in which a somewhat better " over-all " yield (10%) was obtained and which involved the use of an amine more readily obtainable than *m*-anisidine, was also investigated. *Phthalo*-3-*nitro*-p-*anisidide* (XIX), obtained by heating 3-nitro-*p*-anisidine with phthalic anhydride at 160—170°, was reduced to the corresponding *amine* (XX) by means of iron filings and a dilute solution of hydrochloric acid in alcohol. Diazotisation of this amine, followed by reaction with pyridine and hydrolysis of the product, yielded a mixture of 2-amino-5-methoxyphenylpyridines, from which α-2-amino-5-methoxyphenylpyridine (XVIII) was isolated by fractional crystallisation of the mixed picrates from acetone.

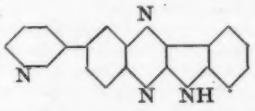
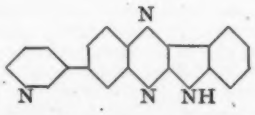
Nitration of 6-methoxy-8-α-pyridylquinoline gave a compound regarded as 5-*nitro*-6-*methoxy*-8-α-*pyridylquinoline* (XXI), which was reduced to the corresponding *amine* (XXII).

In order to prepare a representative pyridylhydroxyquinoline, the following series of reactions has been examined :



α-3-*Nitro*-4-*aminophenylpyridine* (XXIV) was obtained *via* (XXIII). The amino-group of (XXIV) was replaced by hydroxyl by boiling with caustic potash to give (XXVIII); the structure of this was also confirmed by methylation, α-3-nitro-4-methoxyphenylpyridine being obtained identical with that obtained by Haworth, Heilbron, and Hey (J., 1940, 361). (XXVIII) was reduced to the corresponding o-*aminophenol* (XXIX), which on submission to the Skraup reaction afforded 8-*hydroxy*-5-α-*pyridylquinoline* (XXX). In attempting to methylate (XXX) with ethereal diazomethane, a dark red solid, freely soluble in hydroxylic solvents but sparingly soluble in hydrocarbons or chloroform, was obtained instead of the colourless methyl ether anticipated. This behaviour was simulated exactly by 8-hydroxyquinoline, which gave a scarlet solid probably identical with the product described by Lippman and Fleissner (*Monatsh.*, 1889, **10**, 665; cf. also Claus and Howitz, *J. pr. Chem.*, 1890, **42**, 222; 1892, **45**, 256). Having regard to the properties and the disappearance of the colour with acids, betaine structures (XXVII) are suggested for these compounds. When methyl sulphate and alkali were used, the normal methyl ether was formed; it was identified with 8-methoxy-5-α-pyridylquinoline prepared above.

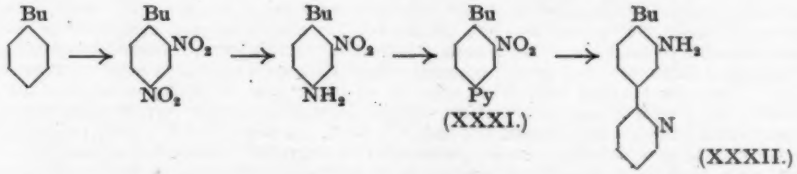
β-4-Acetamidophenylpyridine was nitrated, and the *o*-nitro-compound (cf. XXIII) hydrolysed to β-3-*nitro*-4-*aminophenylpyridine* (cf. XXIV). This constitution was established by reducing (XXIV) to an o-*diamine* which gave *quinoxalines* on condensing with glyoxal, benzil, and isatin, two products (XXV) and (XXVI) being obtained from the last-named dicarbonyl compound:

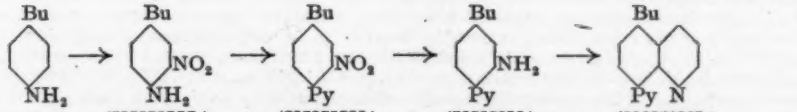
(XXV.)   (XXVI.)

Pyridylalkylquinolines.—The three isomeric 4-aminophenylpyridines were converted by the Doebner–Miller reaction into 6-α-, 6-β-, and 6-γ-*pyridylquinaldine*. Further, condensation of 4-α- and 4-β-aminophenylpyridine with benzaldehyde and pyruvic acid gave 6-α- and 6-β-pyridylatophan (cf. Doebner and Gieseke, *Ber.*, 1887, **20**, 280). The spasmolytic activity of most of these substituted compounds was disappointing and we therefore proceeded to prepare pyridylquinolines carrying an alkyl substituent in the *Bz*-ring of the quinoline residue.

2 : 4-Dinitro-*tert.*-butylbenzene was reduced to 2-nitro-4-amino-*tert.*-butylbenzene; the free amino-group was diazotised and treated with pyridine in the usual manner to give a surprisingly good yield of 3-nitro-4-*tert.*-butylpyridylbenzenes (XXXI). The product was converted into a mixture of picrates and separated by fractional crystallisation into three components. It was only possible to assign provisional orientations to these picrates by comparing relative melting points with those of other series. That assumed to be of β-3-*nitro*-4-tert.-*butylphenylpyridine* was converted into the free base, which was reduced to β-3-*amino*-4-tert.-*butylphenylpyridine* (XXXII), but poor yields at this point compelled us to abandon this series.

4-*tert.*-Butylacetanilide was nitrated, and the acetamido-compound hydrolysed to 2-nitro-4-*tert.*-butylaniline (XXXIII). This base on diazotisation and treatment with pyridine gave 2-nitro-4-*tert.*-butylpyridylbenzene (XXXIV). Reduction and submission of the resulting 2-amino-4-*tert.*-butylpyridylbenzene (XXXV) to the Skraup reaction gave 8-*pyridyl*-5-tert.-*butylquinoline* (XXXVI). As preliminary pharmacological results showed the introduction of the butyl group to have had an unfavourable influence, no attempt was made to separate individual isomerides in this series. These reactions are summarised below:


(XXXI.) (XXXII.)


(XXXIII.) (XXXIV.) (XXXV.) (XXXVI.)

The reaction between aromatic bases and ethyl acetoacetate in many cases leads to good yields of acetoacetanilide or its derivatives; these in turn have frequently been cyclised to methylhydroxyquinolines. We therefore examined the reaction occurring between ethyl acetoacetate and the more readily available pyridylanilides.

4-α-Pyridylaniline failed to react to any useful extent with ethyl acetoacetate when the mixture was heated at 180° for 4 hours. A small yield of *acetoacet*-4-α-*pyridylanilide* was obtained by condensation in boiling xylene solution in presence of phosphorus oxychloride (cf. Coffey, Thompson, and Wilson, J., 1936, 856) or pyridine, but more satisfactory was condensation in presence of excess of acetoacetic ester at 160—170° (Fierz-David and Ziegler, *Helv. Chim. Acta*, 1928, **11**, 779). The β- and the γ-isomeride were obtained similarly. These acetoacetanilides, however, failed to cyclise on heating with sulphuric acid or thionyl chloride. On

heating in absence of condensing agent, s.-*bispyridylphenylureas* and unidentified products were formed; no evidence of the formation of pyridylmethylhydroxyquinolines was found and the investigation was discontinued.

Experimental.

α-3-*Amino*-4-*methoxyphenylpyridine*.—α-3-Nitro-4-methoxyphenylpyridine (27 g.) (Haworth, Heilbron, and Hey, J., 1940, 361) in ethanol (200 c.c.) was reduced with stannous chloride (150 g.) and hydrochloric acid (180 c.c.), a large excess of 30% caustic soda solution added, and the base extracted with ether; distillation at 210—215°/3 mm. gave a pale yellow, viscous liquid (20 g.) which gradually solidified. Crystallisation from light petroleum (b. p. 60—80°) gave α-3-*amino*-4-*methoxyphenylpyridine* in long needles, m. p. 98° (Found: C, 71·8; H, 6·2. $C_{12}H_{12}ON_2$ requires C, 72·0; H, 6·0%). Warming a portion on the steam-bath with acetic anhydride gave α-3-*acetamido*-4-*methoxyphenylpyridine*, which crystallised from benzene–light petroleum (b. p. 60—80°) in needle clusters, m. p. 171—172° (Found: C, 69·3; H, 5·8. $C_{14}H_{14}O_2N_2$ requires C, 69·4; H, 5·8%).

8-*Methoxy*-5-α-*pyridylquinolines*.—α-3-Amino-4-methoxyphenylpyridine (19 g.) was heated with anhydrous glycerol (30 g.), concentrated sulphuric acid (28 g.), and anhydrous arsenic acid (14 g.) at 160—170° for 6 hours, the mass treated as described (preceding paper) for the preparation of 6-α-pyridylquinoline, and the base extracted with benzene. After removal of benzene, distillation at 130—160° in a high vacuum gave a very viscous, brown liquid (16 g.), which was treated with a solution of picric acid (2 mols.) in alcohol. Crystallisation of the product from methyl ethyl ketone gave the pure *picrate* (26 g.) in long prismatic needles, m. p. 196—198° (decomp.) (Found: N, 15·2. $C_{18}H_{12}ON_2,C_6H_3O_7N_3$ requires N, 15·0%). Dilute caustic soda solution liberated 8-*methoxy*-5-α-*pyridylquinoline*, which separated from light petroleum (b. p. 60—80°) in small prisms, m. p. 115—116° (Found: C, 76·4; H, 5·1. $C_{15}H_{12}ON_2$ requires C, 76·3; H, 5·1%).

α-3-*Amino*-6-*methoxyphenylpyridine*.—α-5-Nitro-2-methoxyphenylpyridine (8·8 g.) (Haworth, Heilbron, and Hey, J., 1940, 359) in ethanol (80 c.c.) was reduced with stannous chloride (50 g.) and hydrochloric acid (50 c.c.), 30% caustic soda solution added, and the base extracted with ether. After removal of ether, α-3-amino-6-methoxyphenylpyridine remained as a viscous liquid (7·0 g.), which became semi-solid after 24 hours. Warming a portion with acetic anhydride gave α-3-*acetamido*-6-*methoxyphenylpyridine*, which separated from benzene–light petroleum (b. p. 40—60°) in silky needles, m. p. 168—169° (Found: C, 69·7; H, 5·9. $C_{14}H_{14}O_2N_2$ requires C, 69·4; H, 5·8%).

6-*Methoxy*-5(and 7)-α-*pyridylquinoline*.—α-3-Amino-6-methoxyphenylpyridine (7·0 g.) was heated with anhydrous glycerol (14 g.), concentrated sulphuric acid (13 g.), and anhydrous arsenic acid (7·0 g.). After boiling for 4 hours, the mixture was cooled, diluted with water (2 vols.), filtered after 12 hours, and made alkaline. The precipitated tarry oil was extracted with benzene. After removal of benzene, distillation at 167—180°/0·04 mm. gave a yellowish-brown viscous liquid (4·9 g.). It was treated with picric acid (2 mols.) in ethanol, and the resulting picrates crystallised from acetone. Numerous crystallisations gave a pure *picrate* (3·4 g.) in small prisms, decomp. 222° (Found: N, 15·3. $C_{18}H_{12}ON_2,C_6H_3O_7N_3$ requires N, 15·0%), from which dilute caustic soda solution liberated 6-*methoxy*-5(or 7)-α-*pyridylquinoline*; this crystallised from light petroleum (b. p. 40—60°) in small needles, m. p. 100—101° (Found: C, 76·6; H, 5·2. $C_{15}H_{12}ON_2$ requires C, 76·3; H, 5·1%). From the mother-liquors, a second pure picrate was obtained in hard needles (3·1 g.), m. p. 215—216° (decomp.). 6-*Methoxy*-7(or 5)-α-*pyridylquinoline* separated from light petroleum (b. p. 40—60°) in long prismatic needles, m. p. 95° (after drying at 45° in a high vacuum) (Found: C, 76·4; H, 5·3%).

5-*Amino*-6-*methoxyquinoline*.—6-Methoxyquinoline (38 g.; b. p. 166—167°/22 mm.), prepared from *p*-anisidine (50 g.) by means of the Skraup reaction, was converted into 5-nitro-6-methoxyquinoline (36 g.; m. p. 104—105°) by treatment with fuming nitric acid at 0° (Jacobs and Heidelberger, *loc. cit.*). Reduction with iron filings and alcoholic hydrochloric acid gave 5-amino-6-methoxyquinoline (27 g.; m. p. 153—154°). The constitution of the 5-nitro-6-methoxyquinoline was proved by heating with concentrated hydrochloric acid in a sealed tube for 5 hours at 180°, 5-nitro-6-hydroxyquinoline, m. p. 136—137° (lit., m. p. 136°, 138—139°, 139—140°), being obtained.

Preparation of a Triazen from 5-*Amino*-6-*methoxyquinoline*.—A diazonium solution prepared from 5-amino-6-methoxyquinoline (5 g.) was added slowly with stirring to an aqueous solution of dimethylamine (5 c.c.; 33%) and sodium carbonate (cf. B.P. 513,846). The separated brown solid was purified by passing its benzene solution through a column of alumina. After removal of most of the benzene and addition of light petroleum, the *triazen* separated in pale yellow needles (3·5 g.), m. p. 82—83° (Found: C, 63·0; H, 6·1. $C_{12}H_{14}ON_4$ requires C, 62·6; H, 6·1%).

6-*Methoxy*-8-α(β and γ)-*pyridylquinoline*.—8-Amino-6-methoxyquinoline (20 g.) was dissolved in concentrated hydrochloric acid (25 c.c.) and water (75 c.c.) at 90°, hydrochloric acid (25 c.c.) added, and the whole cooled in a freezing mixture; the paste formed was diazotised at 0—5° with sodium nitrite (8·4 g.). The diazonium solution was stirred during 1½ hours into pyridine (350 g.) at 40—50°, after a further hour's stirring at 40—50° a concentrated solution of caustic soda added, and the pyridine layer separated. Excess of pyridine was removed in steam, and the tarry residue extracted with benzene. After removal of the benzene, distillation at 150—180°/0·002 mm. gave a very viscous, red-brown oil (10·0 g.). This was treated with a hot solution of picric acid (2 mols.) in alcohol, and the resulting mixed picrates crystallised from glacial acetic acid. After several crystallisations, a pure *picrate*, separating in long orange needles (2·8 g.), m. p. 247—248°, was obtained (Found: C, 54·3; H, 3·5; N, 14·7. $C_{15}H_{12}ON_2,C_6H_3O_7N_3$ requires C, 54·2; H, 3·2; N, 15·0%), from which dilute caustic soda solution liberated 6-*methoxy*-8-α-*pyridylquinoline*; this separated from benzene–light petroleum (b. p. 40—60°) in prisms, m. p. 106—107° (Found: C, 76·1; H, 5·1. $C_{15}H_{12}ON_2$ requires C, 76·3; H, 5·1%). The mixed picrates obtained from the mother-liquors were extracted with acetone and from the acetone solution a pure *picrate*, crystallising in needle clusters, m. p. 260° (decomp.), was obtained (Found: C, 54·4; H, 3·2%). Treatment with dilute caustic soda solution liberated 6-*methoxy*-8-γ-*pyridylquinoline*, which separated from benzene–light petroleum (b. p. 60—80°) in small prisms, m. p. 146° (Found: C, 76·2; H, 5·1%). Fractional crystallisation from methyl ethyl ketone of the material remaining after the acetone extraction gave a third pure *picrate* in needle clusters, m. p. 243—244° (Found: N, 14·8%), from which 6-*methoxy*-8-β-*pyridylquinoline* was isolated; it separated from benzene–light petroleum (b. p. 60—80°) in prisms, m. p. 100° (Found: C, 76·5; H, 5·1%). The identity of 8-α- and 8-β-pyridyl-6-methoxyquinoline with the corresponding compounds prepared as described below was shown by means of mixed melting-points.

Nitration of α-3-*Methoxyphenylpyridine*.—To a solution of α-3-methoxyphenylpyridine (4·0 g.) (Haworth, Heilbron, and Hey, J., 1940, 361) in glacial acetic acid (20 c.c.), nitric acid (*d* 1·5; 8 c.c.) was added in small portions. After refluxing for 1 hour, the mixture was cooled and poured into dilute caustic soda solution, and the liquid product extracted with benzene. After removal of solvent the residual oil was treated with alcoholic picric acid, and the resulting picrates crystallised from acetone. Numerous crystallisations gave α-2-*nitro*-5-*methoxyphenylpyridine picrate* in small rectangular prisms, m. p. and mixed m. p. with the corresponding compound prepared as described below, 190—191° (Found: N, 15·0. $C_{12}H_{10}O_3N_2,C_6H_3O_7N_3$ requires N, 15·2%). Fractionation of the more soluble portion of the mixed picrates from benzene gave a second *isomeride* in needle clusters, m. p. 155—156° (Found: N, 15·0%); a third *isomeride*, m. p. 273°, was obtained in orange needles (alcohol) by passing a solution of the remaining material in benzene through a column of alumina and washing with alcohol–benzene (1 : 1) (Found: N, 15·2%).

*Action of Diazotised 4-Nitro-*m*-anisidine on Pyridine.*—4-Nitro-*m*-anisidine (16·5 g.) (Reverdin and Widmer, *Ber.*, 1913, **46**, 4071) was suspended in hydrochloric acid (29 c.c.) and water (24 c.c.) and diazotised with a solution of sodium nitrite (7·1 g.) in water (24 c.c.) at 15°. After removal of insoluble matter, the diazonium solution was added during 1 hour to pyridine (250 c.c.) at 50—55°. Stirring was continued for a further hour at 50—60°. Excess of a concentrated solution of caustic soda was added, the pyridine layer distilled in steam, and the residue extracted with benzene. After removal of benzene, distillation under reduced pressure gave a pale yellow solid (5 g.), b. p. 90—135°/1 mm., and a reddish-brown oil (5 g.), b. p. 135—175°/1 mm. The first fraction crystallised from dilute alcohol in needles, m. p. and mixed m. p. with *p*-nitroanisole 52—53°. The second fraction was treated with alcoholic picric acid and by fractional crystallisation of the resulting mixed picrates from acetone, two pure isomerides were obtained. The less soluble *β-2-nitro-5-methoxyphenylpyridine picrate* separated in fine needles (1·2 g.), m. p. 202—204° (Found : N, 15·0. $C_{12}H_{10}O_3N_2,C_6H_3O_7N_3$ requires N, 15·2%), whereas the more soluble α-2-nitro-5-methoxyphenylpyridine picrate separated in small prisms (1·0 g.), m. p. and mixed m. p. with the corresponding compound prepared as described above 190—191°. On treatment with dilute caustic soda solution the former gave *β-2-nitro-5-methoxypyridine*, which separated from light petroleum (b. p. 60—80°) in needles, m. p. 91—92° (Found : C, 62·6; H, 4·6. $C_{12}H_{10}O_3N_2$ requires C, 62·6; H, 4·3%), and the latter gave *α-2-nitro-5-methoxyphenylpyridine*, which crystallised from benzene–light petroleum (b. p. 60—80°) in long needles, m. p. 76° (Found : C, 62·8; H, 4·5%).

β-2-Nitro-5-methoxyphenylpyridine (0·5 g.) in ethanol (5 c.c.) was reduced with stannous chloride (2·0 g.) and concentrated hydrochloric acid (3 c.c.), excess of 30% caustic soda solution added, and the base extracted with benzene. After removal of solvent, the residue was crystallised from benzene–light petroleum (b. p. 60—80°), *β-2-amino-5-methoxyphenylpyridine* being obtained in small needle clusters, m. p. 131—132° (Found : C, 72·2; H, 6·2. $C_{12}H_{12}ON_2$ requires C, 72·0; H, 6·0%). A solution of this base (0·2 g.) in concentrated hydrochloric acid (0·5 c.c.) and water (0·5 c.c.) was diazotised at 0·5° with a solution of sodium nitrite (0·07 g.) in water (0·5 c.c.). A cold solution of stannous chloride (1 g.) in hydrochloric acid (2 c.c.) was then added and after 1 hour the *β*-2-hydrazino-5-methoxyphenylpyridine was liberated with aqueous sodium hydroxide and extracted with benzene. The product obtained on removal of solvent was dissolved in glacial acetic acid (1 c.c.), and powdered copper acetate (0·4 g.) added. After removal of copper as sulphide, the filtrate was made alkaline and extracted with ether. Removal of the ether from the dried extract left *β*-3-methoxyphenylpyridine as an oil, which was treated with alcoholic picric acid. Crystallisation of the resulting picrates from alcohol yielded *β-3-methoxyphenylpyridine picrate* in needles, m. p. 160—162° (Found : N, 13·5. $C_{12}H_{11}ON,C_6H_3O_7N_3$ requires N, 13·6%).

γ-3-Nitrophenylpyridine, prepared from diazotised *m*-nitroaniline and pyridine (Haworth, Heilbron, and Hey, J., 1940, 353), was reduced to *γ*-3-aminophenylpyridine with stannous chloride and hydrochloric acid (Heilbron, Hey, and Lambert, J., 1940, 1279). The base (0·75 g.) in concentrated sulphuric acid (3 c.c.) and water (30 c.c.) was diazotised at 0—5° with an aqueous solution of sodium nitrite (0·32 g.) and added in a thin stream to a boiling mixture of concentrated sulphuric acid (8 c.c.) and water (10 c.c.). When evolution of nitrogen had ceased, the solution was diluted, neutralised with aqueous caustic soda, and acidified with glacial acetic acid. Crystallisation of the resultant precipitate from alcohol gave *γ-3-hydroxyphenylpyridine* in colourless prisms, m. p. 227—228° (Found : C, 77·0; H, 5·4. $C_{11}H_9ON$ requires C, 77·2; H, 5·3%). The hydroxy-compound (0·2 g.) in ether (50 c.c.) was treated with a large excess of diazomethane in the same solvent and kept overnight. After filtration and evaporation the residual oil was treated with alcoholic picric acid (1 mol.). Crystallisation of the resulting picrate from acetone gave *γ*-3-methoxyphenylpyridine picrate in long prisms, m. p. 202—203°, both alone and mixed with the compound of similar m. p. isolated from the product of the reaction between diazotised *m*-anisidine and pyridine (Haworth, Heilbron, and Hey, J., 1940, 361).

A solution of *α*-2-nitro-5-methoxyphenylpyridine (0·3 g.) in ethanol (5 c.c.) was reduced with stannous chloride (1·5 g.) and concentrated hydrochloric acid (2 c.c.), excess of 30% sodium hydroxide solution added, and the base extracted with ether. A portion of the semi-solid product obtained on removal of the solvent was treated with alcoholic picric acid, and the resulting picrate crystallised from ethanol. *α-2-Amino-5-methoxyphenylpyridine picrate* separated in fine needles, m. p. and mixed m. p. with the corresponding compound prepared as above, 193—194° (Found : N, 16·2. $C_{12}H_{12}ON_2,C_6H_3O_7N_3$ requires N, 16·3%).

6-Methoxy-8-α- and *-β-pyridylquinoline.*—*α*-2-Amino-5-methoxyphenylpyridine (0·2 g.) was refluxed with sulphuric acid (66%, 2·4 g.), glycerol (0·5 g.), and sodium *m*-nitrobenzenesulphonate (0·5 g.) for 6 hours. The mixture was cooled, diluted, filtered, and made alkaline. After 12 hours, the tarry precipitate was extracted with benzene. The viscous oil left on removal of solvent was treated with alcoholic picric acid, and the resulting picrate crystallised from glacial acetic acid. 6-Methoxy-8-*α*-pyridylquinoline picrate was obtained in orange-yellow needles, m. p. and mixed m. p. with the corresponding compound prepared as described above, 247—248°. Treatment of this picrate with dilute sodium hydroxide solution liberated the free base, m. p. 106—107° alone and on admixture with the base of the same m. p. obtained as described above. *β*-2-Amino-5-methoxyphenylpyridine was also submitted to the Skraup reaction. 6-Methoxy-8-*β*-pyridylquinoline yielded a picrate, m. p. 243—244°, both alone and on admixture with the picrate of the same m. p. already described.

2-Amino-5-methoxyphenylpyridine via *3-Nitro-*p*-anisidine.*—Phthalic anhydride (100 g.) and 3-nitro-*p*-anisidine (88 g.) were fused together at 170° for 6 hours. After cooling, the solid cake was powdered and crystallised from glacial acetic acid. *Phthalo-3-nitro-*p*-anisidide* separated in yellow plates (130 g.), m. p. 150° (Found : C, 60·4; H, 3·4. $C_{15}H_{10}O_5N_2$ requires C, 60·4; H, 3·4%). To a solution of the phthaloyl compound (130 g.) in alcohol (1960 c.c.), water (22 c.c.), hydrochloric acid (9 c.c.), and iron filings (130 g.) were added and the whole was refluxed for 24 hours. After being made alkaline, the liquid was filtered, and the sludge extracted with alcohol. *4-Phthalo-3-amino-*p*-anisidide* crystallised from the combined alcoholic filtrate and extracts in yellow needles (88 g.), m. p. 188° (Found : C, 67·0; H, 4·6. $C_{15}H_{12}O_3N_2$ requires C, 67·2; H, 4·5%). Finely powdered 4-phthalo-3-amino-*p*-anisidide (88 g.), suspended in hydrochloric acid (102 c.c.) and water (75 c.c.), was diazotised with sodium nitrite (23 g.) in water (60 c.c.) at 10°. After filtering from a little insoluble matter, the diazonium solution was added during 1½ hours with stirring to pyridine (750 c.c.) at 50—55°. After being stirred for a further hour at 50—55°, the solution was poured into water, and the precipitated oil extracted with benzene. The residue, after removal of benzene, was refluxed for 1 hour with excess of hydrochloric acid. The acid solution was basified, and the precipitated oil extracted with benzene. After removal of the benzene, distillation at 160—170°/<1 mm. gave a red-brown oil (10 g.) which solidified on cooling. This solid was treated with alcoholic picric acid; crystallisation of the resulting mixed picrates from acetone gave *α*-2-amino-5-methoxyphenylpyridine picrate in fine needles, m. p. 193—194° both alone and mixed with the picrate of same m. p. prepared as described above.

5-Nitro-6-methoxy-8-α-pyridylquinoline.—6-Methoxy-8-*α*-pyridylquinoline (2·1 g.) was added in small portions to nitric acid (*d* 1·5; 10 c.c.) at 0°. After a further ½ hour's stirring at 0° the solution was diluted with ice-water and made alkaline. Repeated crystallisation of the precipitate from acetone gave the *nitro*-compound in fine, pale yellow needles, m. p. 192—193° (Found : C, 64·3; H, 3·9. $C_{15}H_{11}O_3N_3$ requires C, 64·1; H, 3·9%).

5-Amino-6-methoxy-8-α-pyridylquinoline.—To a solution of 5-nitro-6-methoxy-8-*α*-pyridylquinoline (1·4 g.) in alcohol (50 c.c.), water (0·3 c.c.), hydrochloric acid (0·2 c.c.), and iron filings (1·7 g.) were added and the whole stirred under

reflux on the steam-bath for 24 hours. After being made alkaline with caustic soda solution, the liquid was filtered, the sludge extracted with alcohol, and the combined extracts and filtrate evaporated to dryness. Crystallisation of the residue from benzene–light petroleum (b. p. 60—80°) gave the *base* in small orange-yellow prisms (0·8 g.), m. p. 124—125° (Found: C, 71·6; H, 5·0. $C_{15}H_{13}ON_2$ requires C, 71·7; H, 5·2%).

6-*Pyridylquinaldine.*—α-4-Aminophenylpyridine (5 g.) was heated with concentrated hydrochloric acid (150 c.c.) and paraldehyde (5 g.) on the steam-bath for several hours and the product was diluted with water (2 vols.), kept overnight, and filtered. The filtrate was made alkaline with dilute caustic soda solution, and the precipitated base extracted with benzene. After removal of benzene, distillation at 160° in a high vacuum gave 6-*α-pyridylquinaldine* as a greenish-yellow solid, which crystallised from light petroleum (b. p. 40—60°) in colourless needles (1·7 g.), m. p. 106—107° (Found: C, 81·9; H, 5·4. $C_{15}H_{12}N_2$ requires C, 81·8; H, 5·4%). β-4-Aminophenylpyridine (15 g.) was similarly treated; after removal of the benzene, distillation at 150°/0·001 mm. gave a viscous brown oil (5 g.), which separated from light petroleum (b. p. 40—60°) in colourless prismatic needles of 6-*β-pyridylquinaldine*, m. p. 65—66° (Found: C, 81·8; H, 5·3%). From γ-4-aminophenylpyridine (3·2 g.), after similar treatment (concentrated hydrochloric acid, 50 c.c.; paraldehyde, 4 g.; distillation of the benzene residue at 150—180° in a high vacuum), a brown-yellow solid was obtained, which was purified by passage of its solution in benzene through a column of alumina. Partial removal of the solvent deposited 6-*γ-pyridylquinaldine* in colourless needles, m. p. 186° (Found: C, 81·8; H, 5·4%).

Pyridylatophans.—α-4-Aminophenylpyridine (5 g.), benzaldehyde (3·1 g.), and pyruvic acid (2·6 g.) were refluxed in ethanol (80 c.c.) for 4 hours. 2-*Phenyl*-6-*α-pyridylquinoline*-4-*carboxylic acid* (1·2 g.) separated from the hot solution. It crystallised from ethanol in needles, m. p. 287—288° (decomp.) (Found: C, 77·0; H, 4·6. $C_{21}H_{14}O_2N_2$ requires C, 77·3; H, 4·3%). 2-*Phenyl*-6-*β-pyridylquinoline*-4-*carboxylic acid*, obtained similarly, crystallised from acetic acid or much ethanol in plates, m. p. 301° (decomp.) (Found: C, 77·8; H, 4·3%).

3-*Nitro*-4-tert.-*butylpyridylbenzenes.*—2-Nitro-4-amino-*tert.*-butylbenzene (48 g.) was suspended in concentrated hydrochloric acid (90 c.c.) and water (60 c.c.) and diazotised at 0° with sodium nitrite (17 g.). The filtered solution was added gradually to pyridine (300 c.c.) at 40—50°. After standing, the upper layer was decanted and a further quantity of pyridine solution was obtained by basifying the lower layer with ammonia. The mixed pyridine solution was treated with sodium hydroxide, and pyridine distilled in steam. The oily residue was extracted with benzene, and the extract distilled, eventually in a vacuum. The nitrobutylpyridylbenzene was obtained as an oil (37 g.), b. p. 190—210°/0·01 mm., and the mixture was converted into a mixture of picrates, which were fractionally crystallised first from acetone and then from methyl ethyl ketone. Three apparently pure *picrates* were obtained (given here in order of increasing solubility): A, probably the β-isomeride, m. p. 217—218° (Found: N, 14·6. $C_{15}H_{16}O_2N_2,C_6H_3O_7N_3$ requires N, 14·4%); B, probably the γ-isomeride, m. p. 231° (decomp.) (Found: N, 14·3%); C, probably the α-isomeride, m. p. 160° (Found: N, 14·5%).

Picrate A (3 g.) was heated on the steam-bath for 2 hours with 5% aqueous sodium hydroxide (25 c.c.). On dilution, extraction with benzene, and distillation of the extract in a vacuum a pure *β(?)-isomeride* of 3-nitro-4-*tert.*-butylpyridylbenzene was obtained as a faintly yellow oil distilling at 130° in a high vacuum (yield, 2 g.) (Found: C, 70·7; H, 6·3. $C_{15}H_{16}O_2N_2$ requires C, 70·3; H, 6·3%). The preceding nitro-compound (2 g.) in ethanol (25 c.c.) was added slowly to stannous chloride (10 g.) in concentrated hydrochloric acid (10 c.c.), and the whole refluxed for 2 hours. Ethanol was removed, and the residue suspended in water (10 c.c.) and basified with 50% aqueous sodium hydroxide. 3-Amino-4-*tert.*-butylpyridylbenzene was extracted with benzene and was obtained, after removal of solvent, as a colourless solid crystallising from benzene.

2-*Nitro*-4-tert.-*butylpyridylbenzene.*—4-Nitro-, 4-amino-, 4-acetamido-, 3-nitro-4-acetamido-, and 3-nitro-4-amino-*tert.*-butylbenzene were prepared according to Gelzer's methods (*Ber.*, 1887, **20**, 3257). The nitroamine (78 g.) in a mixture of concentrated hydrochloric acid (200 c.c.) and water (150 c.c.) was diazotised at 0° with sodium nitrite (27·5 g.) in a little water. The filtered diazo-solution was added slowly to pyridine (490 c.c.), stirring being maintained at 40—50° for 1 hour afterwards. The product was worked up as in the case of the isomeride above to give 2-*nitro*-4-tert.-*butylpyridylbenzene* as an oil, b. p. 170—190°/0·05 mm. (31 g.) (Found: C, 70·4; H, 6·3%).

The preceding nitro-compound (31 g.) in ethanol (250 c.c.) was added slowly to stannous chloride (135 g.) in concentrated hydrochloric acid (100 c.c.), the whole refluxed for 2 hours, the ethanol distilled off, the residue made alkaline with 50% aqueous sodium hydroxide, and the organic base extracted with benzene. The extract was distilled in a vacuum and collected at 136—141°/0·02 mm. to give 2-*amino*-4-tert.-*butylpyridylbenzene* (22 g.) (Found: C, 79·4; H, 8·3. $C_{15}H_{18}N_2$ requires C, 79·5; H, 8·0%). This base (22 g.), 64% aqueous sulphuric acid (146 g.), glycerol (33·5 g.), and sodium *m*-nitrobenzenesulphonate (39 g.) were refluxed with stirring at 160° (bath temperature) for 6·5 hours. The cold solution was filtered, made alkaline with ammonia, and, after standing, the tarry deposit was extracted with benzene. Solvent was removed from the extract, and the residue distilled in a vacuum. 8-*Pyridyl*-5-tert.-*butylquinoline*, distilled repeatedly at 120° in a high vacuum, was a pale yellow oil (Found: C, 82·8; H, 7·0. $C_{18}H_{18}N_2$ requires C, 82·5; H, 6·9%).

A mixture of α-3-nitro-4-aminophenylpyridine (preceding paper) (16 g.), caustic potash (50 g.), and water (100 c.c.) was refluxed for 24 hours, the solution made faintly acid with acetic acid, and the precipitate recrystallised from benzene–light petroleum (b. p. 40—60°). α-3-*Nitro*-4-*hydroxyphenylpyridine* was obtained in yellow needles (11·5 g.), m. p. 125° (Found: C, 61·5; H, 3·6. $C_{11}H_8O_3N_2$ requires C, 61·1; H, 3·7%). Methylation with diazomethane in ether gave α-3-nitro-4-methoxyphenylpyridine, m. p. 85—86°, identical with that prepared by Haworth, Heilbron, and Hey (J., 1940, 361).

α-3-Nitro-4-hydroxyphenylpyridine (11 g.) was dissolved in 5% caustic soda solution (165 c.c.), and sodium hydrosulphite (44 g.) added gradually until no further change in colour took place. The solution was then made slightly acid with glacial acetic acid and thoroughly extracted with ether. After washing and removal of ether, the residue was distilled at 195—197°/0·02 mm. Yield, 6 g. Recrystallisation from alcohol–light petroleum (b. p. 40—60°) gave colourless prisms of solvated material melting constantly at 144°. Recrystallisation from benzene gave silky needles of unsolvated α-3-*amino*-4-*hydroxyphenylpyridine*, m. p. 166—167° (Found: C, 71·2; H, 5·3; N, 15·1. $C_{11}H_{10}ON_2$ requires C, 71·0; H, 5·4; N, 15·1%).

A mixture of α-3-amino-4-hydroxyphenylpyridine (2 g.), 63% sulphuric acid (12 g.), glycerol (2·4 g.), and sodium *m*-nitrobenzenesulphonate (2 g.) was heated in an oil-bath at 160° for 5 hours, the solution cooled and diluted with water (10 c.c.), and 10% caustic soda solution added until no further precipitation took place. After 12 hours, the solid was collected, dried, and recrystallised from benzene–light petroleum, giving pale yellow needles of 8-*hydroxy*-5-*α-pyridylquinoline*. Sublimation at 80° in a high vacuum gave colourless needles (1 g.), m. p. 133·5—134° (Found: C, 76·0; H, 4·7. $C_{14}H_{10}ON_2$ requires C, 75·7; H, 4·5%). The hydroxy-compound (0·2 g.) was added to excess of diazomethane in ether and after 24 hours the deep red solid was collected and recrystallised from benzene, in which it gave a blue solution and was sparingly soluble. The *substance* blackened at 140° but did not melt below 250° (Found: N, 11·5. $C_{15}H_{12}ON_2$ requires N, 11·9%. $C_{15}H_{14}O_2N_2$ requires N, 11·3%). To a solution of the pyridylhydroxyquinoline (0·25 g.) and potassium hydroxide (0·125 g.) in water (3 c.c.), methyl sulphate (0·145 g.) was added. The solution was maintained at 70° for 20 mins., cooled, made strongly alkaline with more caustic potash, and extracted with benzene (charcoal).

The solvent was removed, and the residue converted into the picrate, which, recrystallised from acetone, had m. p. 194—196°, alone or mixed with authentic 8-methoxy-5-α-pyridylquinoline picrate.

Pyridylquinoxalines.—β-4-Acetamidophenylpyridine (11·5 g.), obtained from β-4-nitrophenylpyridine (Heilbron, Hey, and Lambert, J., 1940, 1279), was added gradually to nitric acid (47 c.c., *d* 1·5) at 0° as described for the α-isomer (preceding paper). The product was recrystallised from acetone, giving yellow micro-needles of *β-3-nitro-4-acetamidophenylpyridine* (11 g.), m. p. 169° (decomp.) (Found: N, 16·2. $C_{13}H_{11}O_3N_3$ requires N, 16·3%). This acetyl compound (10 g.) was boiled for 20 minutes with 20% caustic potash solution. The product was collected and recrystallised from methanol, giving orange-red needles of *β-3-nitro-4-aminophenylpyridine* (6·5 g.), m. p. 176—177° (Found: N, 19·65. $C_{11}H_9O_2N_3$ requires N, 19·5%). The preceding nitro-compound (6 g.) in a mixture of ethyl acetate (200 c.c.) and ethanol (24 c.c.) was reduced catalytically with hydrogen and Adams's catalyst (0·2 g.). The solution was filtered, solvent removed in a vacuum, and the residue crystallised from benzene–light petroleum (b. p. 40—60°), giving pale fawn leaflets of *β-3:4-diaminophenylpyridine* (4·6 g.), m. p. 122—123° (Found: C, 71·4; H, 6·0; N, 23·0. $C_{11}H_{11}N_3$ requires C, 71·4; H, 6·0; N, 22·7%). The diamine (1 g.) in water (12 c.c.) was treated with a suspension of glyoxal sodium bisulphite compound (3 g.) in water (5 c.c.), glacial acetic acid (3 c.c.) added, and the mixture heated for 1 hour at 70°. After standing for 1 hour at room temperature, the solution was made alkaline, and the resulting fawn precipitate crystallised from benzene–light petroleum (b. p. 40—60°), giving pale yellow needles of *6-β-pyridylquinoxaline* (0·65 g.), m. p. 144—145° (Found: N, 20·5. $C_{13}H_9N_3$ requires N, 20·3%). To the diamine (0·5 g.) in methanol (3 c.c.) and glacial acetic acid (0·5 c.c.), a solution of benzil (0·5 g.) in methanol (3 c.c.) was added. The mixture was heated at 100° for 10 mins., most of the alcohol removed, the solution made alkaline, and the product crystallised from benzene–light petroleum (b. p. 40—60°), giving colourless prisms of *6-β-pyridyl-2:3-diphenylquinoxaline* (0·4 g.), m. p. 194·5—196·5° (Found: N, 11·8. $C_{25}H_{17}N_3$ requires N, 11·7%). A solution of isatin (1·1 g.) in methanol (20 c.c.) and glacial acetic acid (3 c.c.) was added to a solution of the diamine (1·2 g.) in methanol (6 c.c.) and heated on the steam-bath for 5 hours, a yellow solid separating. The solution was kept overnight and then made alkaline with 10% caustic soda solution, and the product crystallised from *cyclo*hexanone, giving two fractions. These were sublimed in a high vacuum at 160° and recrystallised from aqueous pyridine. Two pure products, both crystallising in yellow needles, m. p. 275—276° (Found: N, 19·0. $C_{19}H_{12}N_4$ requires N, 18·9%), and m. p. 307—308° (decomp.) (Found: N, 18·7%), were obtained.

Pyridylacetoacetanilides.—4-Pyridylaniline (5 g.) was dissolved in xylene (50 c.c.) and heated to boiling. A mixture of ethyl acetoacetate (8 g.), pyridine (4 c.c.), and xylene (75 c.c.) was added during 1 hour, xylene being distilled as fast as the solution was added. Boiling was continued for 45 minutes; on cooling, the acetoacetanilide crystallised. The crude product was washed with ether and recrystallised from xylene. The following were prepared: *α-4-Pyridylacetoacetanilide*, m. p. 136° (Found: N, 11·0. $C_{15}H_{14}O_2N_2$ requires N, 11·0%), *β-4-pyridylacetoacetanilide*, m. p. 154·5° (Found: N, 10·7%), *γ-4-pyridylacetoacetanilide*, m. p. 174° (Found: N, 11·0%). The α-acetoacetanilide (10 g.) was heated at 220° until effervescence ceased. When cold, the hard brown mass was warmed with 16% hydrochloric acid (15 c.c.), again cooled, and the bright yellow solid collected. After treatment with ammonia, *s.-bis-α-4-pyridylphenylurea* crystallised from ethanol in iridescent needles, m. p. 278° (decomp.) (Found: N, 15·3; *M*, cryoscopic in camphor, 364. $C_{23}H_{18}ON_4$ requires N, 15·3%; *M*, 366).

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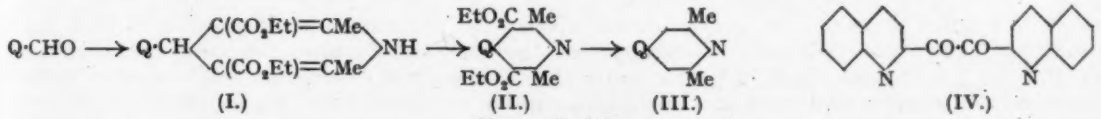
109. *New Therapeutic Agents of the Quinoline Series. Part IV. Lutidylquinolines.*

By A. H. COOK, I. M. HEILBRON, and L. STEGER.

This work comprises further syntheses of compounds of the type of γ-pyridylquinoline. Six quinoline aldehydes, some prepared for the first time by indirect reduction of the corresponding acids, have been converted by the Hantzsch method eventually into γ-2′:6′-dimethylpyridylquinolines. By carrying out the Hantzsch reactions on benzaldehyde with subsequent introduction of an amino-group, or on nitrobenzaldehydes, followed by reduction, aminophenyl-lutidines were obtained; these were submitted to the Skraup reaction. The seven possible γ-2′:6′-dimethylpyridylquinolines were thus prepared.

EARLIER results showed that, of pyridylquinolines isomeric with respect to the orientation of the pyridine nucleus, the γ-compounds were outstanding as spasmolytics. As the preparation of these involved the separation of the α-, β-, and γ-pyridyl compounds as picrates with consequent loss in yield, it was somewhat tedious. We have therefore synthesised the seven possible lutidyl compounds of type (III) by independent methods.

The two main routes were (*a*) subjection of quinoline aldehydes to the Hantzsch synthesis:



(I.) (II.) (III.) (IV.)

(Q = quinolyl)

and (*b*) the preparation of lutidylanilines and their conversion into lutidylquinolines by the Skraup reaction.

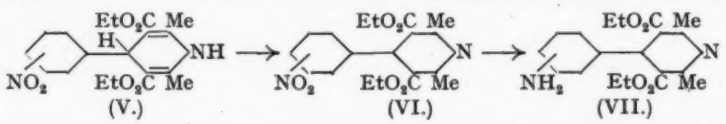
Quinoline-2- and -4-aldehyde, prepared best by oxidising quinaldine and lepidine respectively with fresh selenium dioxide (Kaplan, *J. Amer. Chem. Soc.*, 1941, **63**, 2654), were condensed with ethyl β-aminocrotonate to give the dihydro-esters (I); the product from the 2-aldehyde was accompanied by a yellow fluorescent compound, probably the diketone (IV). Difficulty was experienced in preparing quinoline-6-aldehyde in quantity by the method of Howitz and Philipp (*Annalen*, 1913, **396**, 28) and the rather similar conversion of 8-methylquinoline into quinoline-8-aldehyde by bromination, hydrolysis, and oxidation of 8-hydroxymethylquinoline eventually obtained, was found to be impracticable. Oxidation of methylquinolines with chromyl chloride, of methylquinolines (other than the 2- and the 4-isomeride) with selenium dioxide, or interaction of quinoline with methylformanilide and phosphorus oxychloride all failed to yield quinoline aldehydes. We also attempted to

couple diazotised aminoquinolines with cinnamic acid (cf. Meerwein, *J. pr. Chem.*, **1939**, **159**, 256) whereby phenylquinolylethylenes which could be oxidised to aldehydes might have resulted; coupling in the expected manner did not take place and, from 8-amino-6-methoxyquinoline, for example, a good yield of 8-chloro-6-methoxyquinoline was obtained by a remarkably facile Sandmeyer reaction.

Eventually the difficulty was overcome by preparing quinoline-6- and -8-, as well as the hitherto unknown -3- and -5-aldehydes, by reducing the appropriate carboxylic acid by way of the hydrazide and its toluenesulphonyl compound (cf. McFayden and Stevens, J., **1936**, 584; Pannizzon, *Helv. Chim. Acta*, **1941**, **24**, 24).

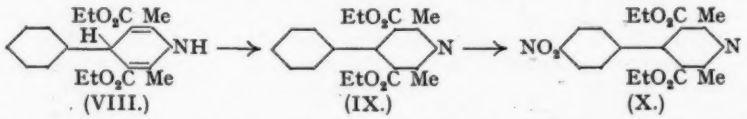
Each of these aldehydes was converted into the dihydro-esters (I) either with ethyl β-aminocrotonate or, in the case of the 3-, 5-, and 8-isomerides, preferably with ethyl acetoacetate and alcoholic ammonia. All these dihydro-esters were unaffected by nitrous acid or ethyl nitrite (cf. Lepetit, *Ber.*, 1887, **20**, 1340), but were smoothly oxidised by warm dilute nitric acid to the esters (II); with all except the 6-ester, 2N-nitric acid was sufficient; in this case 4N-nitric acid induced further reaction, probably hydrolysis, but oxidation was uncomplicated when 3N-acid was used. The lutidyldicarboxylic esters were hydrolysed with caustic alkali; the free acids were readily soluble in water and insoluble in organic extractants and so were not usually purified. Decarboxylation by heating the alkali salts with soda-lime could not be satisfactorily effected, nor was the action of heat on mixtures of the free acid with copper bronze successful. The lutidylquinolines were ultimately obtained in good yield by heating the moist silver salts of the carboxylic acids in a vacuum. All were highly crystalline compounds.

Whilst the above difficulties were being overcome, we investigated the preparation and usefulness of lutidylanilines. *o-*, *m-*, and *p*-Nitrobenzaldehyde had been condensed with ammonia and ethyl acetoacetate to give the esters (V) (cf. Lepetit, *Ber.*, 1887, **20**, 1338; Hinkel, Ayling, and Morgan, J., **1931**, 1835). We obtained the *m-* and the *p*-nitro-ester (V) in much improved yield by condensing the aldehydes with ethyl β-aminocrotonate in absence of solvent. All three esters were smoothly oxidised to the lutidyl derivatives (VI) by dilute nitric acid. The *m-* and the *p*-ester were reduced with tin and hydrochloric acid to the corresponding amines (VII), but the *o*-nitro-ester was resistant to reduction; since the preparation of 8-lutidylquinoline had already



been accomplished, this second route to the same compound was then abandoned. The *m-* and the *p*-amino-ester were hydrolysed, and the acids decarboxylated, best by dry distillation with copper powder, the method of heating moist silver salts being unsuccessful in this series. In this way we obtained 4-m- and -p-*aminophenyl*-2 : 6-*lutidine*. The latter underwent the Skraup reaction to give 6-2′ : 6′-*lutidylquinoline* identical with that already prepared *via* quinoline-6-aldehyde, but *m*-aminophenyl-lutidine on being submitted to the same reaction afforded two isomerides; one, formed in preponderating amount, was identical with 5-2′ : 6′-lutidylquinoline and the second product must therefore have been the remaining 7-2′ : 6′-*lutidylquinoline*. There appears little doubt that the product, m. p. 109°, obtained by Lepetit (*Gazzetta*, **1887**, **17**, 474) was a mixture of these two isomerides.

Inconvenience attached to the preparation of *p*-nitrobenzaldehyde led us to examine the nitration of phenyl-lutidinedicarboxylic ester (IX). Benzaldehyde and ethyl β-aminocrotonate afforded an extremely good yield of the ester (VIII); this was oxidised by warm dilute nitric acid to the lutidine derivative (IX), which was then treated with fuming nitric acid in concentrated sulphuric acid. The crude nitro-compounds



in alcoholic solution deposited the pure *p*-nitro-compound (X), identical with that prepared from *p*-nitrobenzaldehyde, in 33% yield on cooling; by nitrating at −20°, the yield of *p*-nitro-compound was raised to 60%.

Of the above lutidylquinolines, the most easily accessible was the 6-isomeride and in view of promising biological results, we attempted to obtain it by the interaction of 6-nitrosoacetamidoquinoline with 2 : 6-lutidine. Reaction was normal, though only a small yield of 6-lutidylquinoline was isolated; fractionation of the picrate of this product gave only one pure compound and since it was isomeric with the base previously obtained, it was formulated as 6-β-2′ : 6′-dimethylpyridylquinoline.

Experimental.

2-γ-2′ : 6′-*Dimethylpyridylquinoline*.—Quinoline-2-aldehyde (3 g.) or an equivalent quantity of the monohydrate and ethyl β-aminocrotonate (5 g.) were heated on the steam-bath for 3 hours. The viscous oil was washed with a little ether to cause it to solidify, and the crystalline product collected. The *ethyl* 4-2′-*quinolyl*-2 : 6-*dimethyldihydropyridine*-3 : 5-*dicarboxylate* (2·36 g.) was crystallised from ethanol and later from benzene to yield almost colourless plates, m. p. 190° (Found : N, 7·4; *M*, cryoscopic in camphor, 355. $C_{22}H_{24}O_4N_2$ requires N, 7·3%; *M*, 366). When heating was prolonged in the original preparation, a more soluble yellow compound with a green fluorescence was formed. This crystallised from ethanol in yellow plates, m. p. 159°, and was probably 2 : 2′-diquinolylglyoxal. The dihydro-compound (5 g.) was treated with 2N-nitric acid (40 c.c.), and the suspension heated to boiling. The yellow nitrate passed into

solution with evolution of nitrous fumes and after 15 minutes the clear solution was poured into water (200 c.c.) and basified with sodium hydroxide. The *ethyl* 4-2′-*quinolyl*-2 : 6-*dimethylpyridine*-3 : 5-*dicarboxylate* separated from aqueous ethanol in small white needles, m. p. 91°, readily soluble in ethanol or benzene (Found : C, 69·4; H, 5·5. $C_{22}H_{22}O_4N_2$ requires C, 69·8; H, 5·8%). This quinolyl-lutidinedicarboxylic ester (1·5 g.) was refluxed for 4 hrs. with potassium hydroxide (3·5 g.) in ethanol (10 c.c.). The solution was cooled, and the crystalline potassium salt collected and redissolved in the minimum quantity of water. The solution was precipitated with aqueous silver nitrate. The precipitated silver salt (0·85 g.) was gradually heated to 300—400°/15 mm. The liquid distillate was extracted with benzene (10 c.c.), and the solvent then removed from the extract to leave a crystalline mass of 2-*lutidylquinoline* (0·2 g.). The base, recrystallised from light petroleum, gave white needles, m. p. 135° (Found : N, 12·1. $C_{16}H_{14}N_2$ requires N, 12·0%). The *picrate*, prepared from alcoholic solutions of the components and crystallised from acetone–alcohol, had m. p. 230° (decomp.) (Found : N, 15·3. $C_{16}H_{14}N_2,C_6H_3O_7N_3$ requires N, 15·1%).

3-γ-2′ : 6′-*Dimethylpyridylquinoline*.—Quinoline-3-carboxylic ester (Gilman and Spatz, *J. Amer. Chem. Soc.*, 1941, **63**, 1556) (17 g.) was refluxed at 110° for 4 hrs. with 50% hydrazine hydrate (12 g.). After cooling, the pale yellow solid was collected and washed with water; *quinoline*-3-*carboxyhydrazide* formed colourless needles, m. p. 190°, from ethanol (Found : N, 22·5. $C_{10}H_9ON_3$ requires N, 22·5%). The hydrazide (12·5 g.) was dissolved in pyridine (70 c.c.), and *p*-toluenesulphonyl chloride (14 g.) added slowly. Excess of pyridine was removed in a vacuum, water added to the residue, and the p-*toluenesulphonyl* derivative (21 g.) crystallised from *cyclo*hexanone–ethanol; it had m. p. 232° (decomp.) (Found : N, 12·5. $C_{17}H_{15}O_3N_3S$ requires N, 12·3%). The toluenesulphonyl derivative (20 g.) was dissolved in glycol (100 c.c.) at 100°, and anhydrous sodium carbonate (20 g.) added, the temperature being maintained at 160° for 3 mins. The product was cooled, diluted with water, and extracted with ether. *Quinoline*-3-*aldehyde* (3 g.) was extracted; it was sublimed in a vacuum and then crystallised from water, forming colourless needles, m. p. 70° (Found : N, 8·8. $C_{10}H_7ON$ requires N, 9·0%). The aldehyde (1·8 g.), ethyl acetoacetate (3·24 g.), and 3% alcoholic ammonia (7 c.c.) were heated in a sealed tube for 7 hrs. at 100°. After removal of solvent and crystallisation of the residue from benzene, *ethyl* 4-3′-*quinolyl*-2 : 6-*dimethyldihydropyridine*-3 : 5-*dicarboxylate* was obtained in long colourless needles, m. p. 193° (yield, 79%) (Found : N, 7·2. $C_{22}H_{24}O_4N_2$ requires N, 7·4%). The preceding dihydro-ester (2·7 g.) was boiled for 10 mins. with 2N-nitric acid (11 c.c.), and the liquid then made alkaline. When the brown solid was crystallised from light petroleum, *ethyl* 4-3′-*quinolyl*-2 : 6-*dimethylpyridine*-3 : 5-*dicarboxylate* was obtained in colourless rhombs (2·3 g.), m. p. 77° (Found : C, 70·1; H, 5·8; N, 7·4. $C_{22}H_{22}O_4N_2$ requires C, 69·8; H, 5·8; N, 7·4%). This ester (1·5 g.) was added to potassium hydroxide (2·3 g.) in ethanol (8 c.c.), and the solution refluxed for 12 hrs.; a little acetic acid was then added to neutralise free alkali, and the silver salt of the corresponding dicarboxylic acid (2·3 g.) precipitated with silver nitrate. On heating in a vacuum, the slightly moist silver salt gave a distillate of crude 4-*lutidylquinoline* (0·5 g.; 50%). After subliming in a vacuum and crystallising from light petroleum, it formed colourless needles, m. p. 100° (Found : N, 11·8. $C_{16}H_{14}N_2$ requires N, 12·0%).

4-γ-2′ : 6′-*Dimethylpyridylquinoline*.—Quinoline-4-aldehyde (0·2 g.) was heated for 2 hrs. at 100° with ethyl β-aminocrotonate (0·4 g.). The brown liquid, on cooling and scratching with ether, gave *ethyl* 4-4′-*quinolyl*-2 : 6-*dimethyldihydropyridine*-3 : 5-*dicarboxylate* (0·2 g.). This separated in white crystals, m. p. 200°, from benzene (Found : C, 69·3; H, 6·1; N, 7·4. $C_{22}H_{24}O_4N_2$ requires C, 69·5; H, 6·3; N, 7·4%). This ester (5 g.) was boiled with 2N-nitric acid (20 c.c.) for 15 mins., the liquid made alkaline, and the *ethyl* 4-4′-*quinolyl*-2 : 6-*dimethylpyridine*-3 : 5-*dicarboxylate* (4·5 g.) collected; it had m. p. 122° (Found : C, 69·8; H, 5·6. $C_{22}H_{22}O_4N_2$ requires C, 69·8; H, 5·8%). The above dicarbethoxypyridylquinoline (4 g.) was added to a solution of potassium hydroxide (6 g.) in ethanol (20 c.c.) and refluxed for 4 hrs. The liquid was cooled, and the crystalline potassium salt collected (yield, theoretical). The silver salt was prepared and decarboxylated as in the case of the 2-isomeride, 4 g. yielding 1·0 g. of 4-*lutidylquinoline* (58%), which separated from light petroleum in colourless crystals, m. p. 122° (Found : N, 11·9. $C_{16}H_{14}N_2$ requires N, 12·0%).

5-γ-2′ : 6′-*Dimethylpyridylquinoline*.—*m*-Aminobenzoic acid (100 g.), nitrobenzene (60 g.), glycerol (220 g.), boric acid (25 g.), and concentrated sulphuric acid (140 c.c.) were heated under reflux until reaction commenced; when the reaction had subsided, the whole was boiled for 14 hrs., diluted with 1 vol. of water, and strongly basified with sodium hydroxide. The black tar was decanted, and the clear solution acidified with acetic acid. Quinoline-5-carboxylic acid (yield, 95%; m. p. 350° with decomp.) was collected and dried at 120°. The finely powdered acid (10 g.) was refluxed with thionyl chloride (30 c.c.) for 3 hrs. After removal of the excess of thionyl chloride in a vacuum ethanol (20 c.c.) was added to the residue, and the whole refluxed for 30 mins. The clear liquid was poured on ice and made alkaline with ammonia, and the ester extracted with ether. On removal of solvent and distillation of the residue *ethyl quinoline*-5-*carboxylate* (9 g.) was collected as an oil, b. p. 190—192°/15 mm., m. p. 10° (Found : N, 6·5. $C_{12}H_{11}O_2N$ requires N, 7·0%). The ester (9 g.) was refluxed with 50% hydrazine hydrate (6·75 g.) for 2 hrs., the clear liquid allowed to cool, and the solid collected and washed with water. Quinoline-5-carboxyhydrazide, crystallised from ethanol, had m. p. 169°. The *toluenesulphonyl* derivative, prepared by the same method as was used for the 3-isomeride, separated from ethanol apparently as an alcoholate which lost solvent of crystallisation at 180°, thus affording the pure compound, m. p. 200° (Found : N, 12·4. $C_{17}H_{15}O_3N_3S$ requires N, 12·3%).

The crude *p*-toluenesulphonylhydrazide (25 g.), dissolved in glycol (125 c.c.), was heated to 100°, and anhydrous sodium carbonate (25 g.) added as rapidly as possible. The temperature was maintained at 160° for 3 mins., water then added, and the filtrate extracted three times with ether. After removal of solvent and sublimation of the residue in a vacuum, *quinoline*-5-*aldehyde* (1·5 g.) was obtained; it separated from water in colourless needles, m. p. 96° (Found : N, 8·8. $C_{10}H_7ON$ requires N, 8·9%).

Quinoline-5-aldehyde (1 g.), ethyl acetoacetate (1·65 g.), and a solution of ammonia (0·12 g.) in ethanol (5 c.c.) were heated for 7 hrs. at 100° (sealed tube). The solvent was removed by evaporation, and the yellow crystalline residue recrystallised from benzene, yielding *ethyl* 4-5′-*quinolyl*-2 : 6-*dimethyldihydropyridine*-3 : 5-*dicarboxylate* in colourless rhombs, m. p. 201° (yield, 1·2 g.; 52%) (Found : N, 7·2. $C_{22}H_{24}O_4N_2$ requires N, 7·4%). When the dihydro-ester (1 g.) was added to boiling 2N-nitric acid (4 c.c.) and heating continued, a clear orange liquid was obtained. When this was made alkaline, *ethyl* 4-5′-*quinolyl*-2 : 6-*dimethylpyridine*-3 : 5-*dicarboxylate* was precipitated; it separated in colourless rhombs, m. p. 79°, from light petroleum (Found : C, 70·1; H, 5·8; N, 7·4. $C_{22}H_{22}O_4N_2$ requires C, 69·8; H, 5·9; N, 7·4%). The ester (0·4 g.) was added to potassium hydroxide (0·6 g.) in ethanol (2 c.c.), and the solution refluxed for 10 hrs., then cooled and the yellowish salt collected and washed with ethanol. The silver salt was prepared, and heated in a vacuum. The yellow sublimate was extracted with hot benzene, the extract filtered, benzene removed from the filtrate, and the residue sublimed in a vacuum. 5-2′ ; 6′-*Lutidylquinoline* separated from light petroleum in colourless rhombs, m. p. 151° (yield, 54%) (Found : N, 12·3. $C_{16}H_{14}N_2$ requires N, 12·0%). The picrate separated from ethanol in yellow needles, m. p. 231—234° (Found : N, 15·2. $C_{16}H_{14}N_2,C_6H_3O_7N_3$ requires N, 15·1%). It was identical with the product obtained from *m*-nitrobenzaldehyde as described below.

6-γ-2′ : 6′-*Dimethylpyridylquinoline*.—(*a*) Ethyl 4-*p*-nitrophenyl-2 : 6-dimethyldihydropyridine-3 : 5-dicarboxylate was best prepared by heating *p*-nitrobenzaldehyde (38 g.) on the steam-bath for 5 hrs. with ethyl β-aminocrotonate (64 g.). The viscous product crystallised on rubbing and was recrystallised from ethanol; m. p. 136° (yield, 52 g.; 56%) (cf. Hinkel, Ayling, and Morgan, J., 1931, 1835). The dihydropyridine ester (22 g.) was heated with 2N-nitric acid

(88 c.c.) until nitrous fumes were no longer evolved; the solution was then diluted with an equal volume of water and made alkaline with caustic alkali, and the *ethyl* 4-p-*nitrophenyl*-2 : 6-*dimethylpyridine*-3 : 5-*dicarboxylate* collected; it separated from ethanol in pale yellow needles (20 g.), m. p. 115° (Found : C, 61·9; H, 5·3; N, 7·7. $C_{19}H_{20}O_6N_2$ requires C, 61·8; H, 5·4; N, 7·5%). This nitrophenylpyridine ester (15 g.) was heated for 2 hrs. at 100° with granulated tin (7 g.), concentrated hydrochloric acid (40 c.c.), and water (20 c.c.); the clear red solution was poured into an excess of sodium hydroxide solution, *ethyl* 4-p-*aminophenyl*-2 : 6-*dimethylpyridine*-3 : 5-*dicarboxylate* extracted with ether, and the extract evaporated (yield, 13 g.; 95%). The amino-compound separated from ethanol in yellow plates, m. p. 145° (Found : N, 8·4. $C_{19}H_{22}O_4N_2$ requires N, 8·2%). The amino-ester (8 g.) was added to potassium hydroxide (11 g.) in ethanol (40 c.c.), and the solution heated under reflux for 4 hrs., then cooled, and the potassium salt collected, washed with ethanol, and dried (yield, 9 g.; 100%). The silver salt was precipitated by adding a slight excess of silver nitrate to an aqueous solution of the potassium salt. 4-*p*-Aminophenyl-2 : 6-dimethylpyridine-3 : 5-dicarboxylic acid was obtained by suspending the silver salt (5 g.) in water (60 c.c.) and decomposing it with hydrogen sulphide. After removal of silver sulphide the filtrate was evaporated until crystallisation set in, cooled, and the free acid collected. It formed yellow plates, m. p. above 360°, almost insoluble in all the usual solvents except water. The free acid (0·5 g.) was heated with copper powder (2 g.) in a high vacuum over a naked flame, the red oily distillate diluted with chloroform and filtered, and solvent removed. The yellow residue was extracted with boiling light petroleum; when the solution was cooled, 4-p-*aminophenyl*-2 : 6-*dimethylpyridine* was deposited in white needles (0·15 g.), m. p. 131° (Found : N, 14·4; *M*, cryoscopic in camphor, 191. $C_{13}H_{14}N_2$ requires N, 14·1%; *M*, 198). In a larger run, 16 g. of the dicarboxylic acid and 30 g. of copper powder gave 7 g. of aminophenyl-lutidine, m. p. 131° (yield, 63%). *p*-Aminophenyl-lutidine (4·8 g.) was boiled for 4 hrs. with glycerol (10 g.), 66% sulphuric acid (45 g.), and sodium *m*-nitrobenzenesulphonate (10 g.). The solution was diluted, filtered, made alkaline, and extracted twice with benzene (70 c.c. portions); the extract was evaporated, and the residue distilled in a vacuum. 6-*Lutidylquinoline* distilled at 220—230°/15 mm. (yield, 4·0 g.; 71%) and solidified to a mass of pale yellow crystals; recrystallised from light petroleum, it formed white needles, m. p. 84° (Found : N, 12·0. $C_{16}H_{14}N_2$ requires N, 12·0%). The *picrate* separated from *cyclo*hexanone–ethanol in needles, m. p. 224—225° (Found : N, 15·3. $C_{16}H_{14}N_2,C_6H_3O_7N_3$ requires N, 15·1%).

Ethyl 4-phenyl-2 : 6-dimethyldihydropyridine-3 : 5-dicarboxylate (Knoevenagel, *Ber.*, 1898, **31**, 738) was oxidised with boiling 2N-nitric acid as above. The resulting lutidine ester (85 g.) was finely powdered and added slowly to concentrated sulphuric acid (150 c.c.) below −20°. The solution was treated dropwise with nitric acid (*d* 1·4, 40 c.c.) with cooling, the mixture kept for 2 hrs. longer, poured on ice (1000 g.), and made alkaline, and the semi-solid mass of nitrolutidine ester separated, washed by decantation, and dissolved in the minimum quantity of boiling ethanol. On cooling, ethyl 4-*p*-nitrophenyl-2 : 6-dimethylpyridine-3 : 5-dicarboxylate, m. p. 115° (62 g.; 60%), separated. It was identical with the product prepared from *p*-nitrobenzaldehyde.

(*b*) Ethyl quinoline-6-carboxylate (Einhorn, *Ber.*, 1909, **42**, 4854) (40 g.) was heated with 50% hydrazine hydrate (30 g.) for 2 hours at 110°. On cooling, quinoline-6-carboxyhydrazide solidified; after being washed with water, it had m. p. 188° (yield, 35 g.). The p-*toluenesulphonyl* derivative, prepared from the hydrazide (6·2 g.) and *p*-toluenesulphonyl chloride (7 g.), formed white crystals, m. p. 218° (decomp.), from *cyclo*hexanone (Found : N, 12·2. $C_{17}H_{15}O_3N_3S$ requires N, 12·3%). The toluenesulphonyl compound (30 g.) in glycol (130 c.c.) was heated to 150°, and anhydrous sodium carbonate (30 g.) rapidly added. Much frothing took place and after 3 minutes the liquid was poured into hot water, cooled, filtered, and extracted with ether. On removal of the extractant quinoline-6-aldehyde (6·1 g.; 45%) remained; it had m. p. 72° and was identical with that prepared previously (cf. Howitz and Philipp, *Annalen*, 1913, **396**, 281).

Quinoline-6-aldehyde (0·2 g.) was heated for 2 hrs. at 100° with ethyl β-aminocrotonate (0·4 g.). On cooling, washing with ether, and crystallisation from benzene, *ethyl* 4-6′-*quinolyl*-2 : 6-*dimethyldihydropyridine*-3 : 5-*dicarboxylate* (0·33 g.), m. p. 209°, was obtained (Found : N, 7·3. $C_{22}H_{24}O_4N_2$ requires N, 7·4%). This dihydropyridine compound (1 part) was boiled with 3N-nitric acid (4 parts) until no more nitrous fumes were evolved, and the solution was diluted with an equal volume of water and made alkaline. The *ethyl* 4-6′-*quinolyl*-2 : 6-*dimethylpyridine*- 3 : 5-*dicarboxylate*, recrystallised from light petroleum (charcoal), formed white needles, m. p. 97° (Found : C, 69·6; H, 5·7. $C_{22}H_{22}O_4N_2$ requires C, 69·8; H, 5·8%). This ester (2 g.) was boiled with potassium hydroxide (3 g.) in ethanol (20 c.c.) for 10 hrs. and the potassium salt (2 g.), which separated on cooling, was collected. The silver salt was heated in a vacuum as in earlier examples for 1 hr. From the distillate was obtained 6-lutidylquinoline, m. p. 84°, identical with the earlier preparation.

6-β-2′ : 6′-*Dimethylpyridylquinoline*.—64% Sulphuric acid (750 g.), *p*-nitroaniline (70 g.), sodium *m*-nitrobenzenesulphonate (200 g.), glycerol (175 g.), and vanadium pentoxide (2 g.) were refluxed at 145° for 1 hour. Working-up in the usual manner, followed by crystallisation, gave 6-nitroquinoline (62 g.), m. p. 149—150°. 5-Acetamidoquinoline (22 g.) was dissolved in glacial acetic acid (160 c.c.) containing acetic anhydride (68 c.c.) and phosphoric oxide (*ca.* 0·3 g.), and the solution stirred at 5—10° while nitrosyl chloride (14 g.) in acetic anhydride (14 g.) was added (½ hr.). The yellow solution was stirred for a further ½ hr., poured on ice, and the product salted out with potassium acetate (250 g.). The solid nitrosoacylamine was collected, dried, and used directly. Half the product of the last reaction was added gradually with stirring to 2 : 6-lutidine (60 g.) at 70°, nitrogen being evolved. The dark-coloured solution was made alkaline, the lutidine distilled in steam, and the residue thoroughly extracted with warm benzene. Washing, drying and removal of solvent gave a black viscous oil, which was distilled at low pressure. Mixed 6-2′ : 6′-lutidylquinolines were obtained as a dark-coloured glass (3 g.), b. p. 190—205°/0·002 mm. They were converted into the picrates, and the product crystallised six times from glacial acetic acid, yielding a *picrate* in yellow needles, m. p. *ca.* 243° (much decomp. beginning at 230°) (Found : N, 15·3. $C_{16}H_{14}N_2,C_6H_3O_7N_3$ requires N, 15·1%). Regeneration of the base gave 6-β-2′ : 6′-*dimethylpyridylquinoline*, crystallising from petroleum (b. p. 40—60°) or ether in needles, m. p. 68° (Found : C, 81·9; H, 5·9. $C_{16}H_{14}N_2$ requires C, 82·0; H, 6·0%).

7 (and 5)-γ-2′ : 6′-*Dimethylpyridylquinoline*.—*m*-Nitrobenzaldehyde (6 g.) and ethyl β-aminocrotonate (10 g.) were heated at 100° for 5 hrs. The product was cooled, and the hard yellow mass crystallised from ethanol. The dihydropyridine (yield, 14 g.; 80%) had m. p. 103°. The dihydro-ester (50 g.) was warmed with 2N-nitric acid (200 c.c.) until vigorous reaction set in, on completion of which the product was poured into cold water (300 c.c.), and the whole made alkaline. The product (yield, theoretical) crystallised from ethanol in white needles of ethyl 4-3′-nitrophenyl-2 : 6-dimethylpyridine-3 : 5-dicarboxylate, m. p. 63° (Lepetit, *Ber.*, 1887, **20**, 1340, gives m. p. 64°). The foregoing ester was reduced to the amino-compound with tin and hydrochloric acid (cf. Lepetit, *loc. cit.*) (yield, 80%). Ethyl 4-3′-aminophenyl-2 : 6-dimethylpyridine-3 : 5-dicarboxylate was hydrolysed in the same manner as the 4′-amino-isomeride above; the slightly moist acid (18 g.) was mixed with copper powder (30 g.) and heated in five portions in a vacuum in a hard glass tube over a free flame. The bulked yellow viscous distillate soon solidified and was crystallised from light petroleum (b. p. 100—120°). *m*-Aminophenyl-lutidine formed needles, m. p. 117° (lit., 110°) (yield, 9·0 g.; 73%) (Found : N, 14·0. Calc. for $C_{13}H_{14}N_2$: N, 14·1%). *m*-Aminophenyl-lutidine (3·1 g.), 66% sulphuric acid (30 g.), glycerol (7 g.), and sodium *m*-nitrobenzenesulphonate (6 g.) were refluxed for 4 hours, the product diluted and filtered, and the filtrate made alkaline. The hot liquid was extracted with benzene (2 × 70 c.c.), the extractant evaporated, and the residue distilled in a vacuum. The mixed lutidylquinolines were collected at 220—230°/15 mm., and soon solidified to a pale yellow mass, m. p. 98—110° (yield, 2·4 g.; 60%); the yield was poorer (*ca.* 33%) when arsenic acid was used. The mixture (2·6 g.) was treated

with picric acid (2·6 g.), each being dissolved in hot ethanol (25 c.c.); the mixed picrates which separated on cooling (5·1 g., m. p. 188—209°) were fractionally crystallised from glacial acetic acid to give two pure *isomerides*: (*a*) Less soluble (3·3 g.), m. p. 223° (Found: N, 15·0. $C_{16}H_{14}N_2,C_6H_3O_7N_3$ requires N, 15·1%). This picrate (2·2 g.) was warmed with 10% sodium hydroxide solution (25 c.c.), and the liberated base extracted with benzene; 0·9 g. of slightly discoloured crystals, m. p. 120—122°, were obtained which on recrystallising from light petroleum gave 7-*lutidylquinoline* in rhombs, m. p. 125° (Found: N, 11·9. $C_{16}H_{14}N_2$ requires N, 12·0%). (*b*) More soluble (0·1 g.), m. p. 231—234° (Found: N, 15·55%); on regeneration as in the previous preparation 5-*lutidylquinoline* was obtained; it separated in hard white crystals, m. p. 151°, from light petroleum (Found: N, 12·3%). It was identified with the product prepared from quinoline-5-carboxylic acid above.

8-*γ*-2′ : 6′-*Dimethylpyridylquinoline*.—Quinoline-8-carboxylic acid (22 g.) was added slowly to thionyl chloride (40 c.c.), and the mixture refluxed for 4 hrs. The excess of chloride was removed in a vacuum, ethanol (60 c.c.) added to the residue, and the product again refluxed for 2 hrs., then poured on ice and made alkaline; *ethyl quinoline*-8-*carboxylate* was liberated as an oil. It was extracted with ether and eventually distilled in a vacuum; it had b. p. 194—197°/13 mm., solidifying to form white needles, m. p. 45° (Found: N, 7·2. $C_{12}H_{11}O_2N$ requires N, 7·0%). *Quinoline*-8-*carboxyhydrazide* was prepared as above; it formed a pale yellow mass, which was extracted from the aqueous medium by hot benzene; addition of light petroleum gave needles, m. p. 99° (Found: N, 21·9. $C_{10}H_9ON_3$ requires N, 22·5%). The *toluenesulphonyl* derivative of the hydrazide separated in pale yellow rhombs, m. p. 187°, from ethanol (yield, 80%) (Found: N, 12·3. $C_{17}H_{15}O_3N_3S$ requires N, 12·3%). When this was submitted to the usual reaction with sodium carbonate in glycol, quinoline-8-aldehyde was obtained in 25% yield. Quinoline-8-aldehyde (1·03 g.), ethyl acetoacetate (1·8 g.), and ammonia (0·15 g.) in ethanol (4 c.c.) were heated for 7 hours at 100° (sealed tube), ethanol removed, the brown residue dissolved in benzene (50 c.c.), and the solution filtered through a column of activated alumina (15 cm. × 1·5 cm. diameter). *Ethyl* 4-8′-*quinolyl*-2 : 6-*dimethyldihydropyridine*-3 : 5-*dicarboxylate* was adsorbed as a yellow band, eluted with a mixture of benzene (90 c.c.) and ethanol (10 c.c.). It crystallised from the same solvent in orange plates, m. p. 161° (Found: N, 7·1. $C_{22}H_{24}O_4N_2$ requires N, 7·4%). The dihydro-ester (0·6 g.) was boiled for 5 mins. with 2N-nitric acid (2·4 c.c.), and the clear yellow solution cooled and made alkaline. The oily deposit soon solidified and was recrystallised from aqueous ethanol; *ethyl* 4-8′-*quinolyl*-2 : 6-*dimethylpyridine*-3 : 5-*dicarboxylate* (0·5 g.) separated in plates, m. p. 80° (Found: C, 70·3; H, 6·1. $C_{22}H_{22}O_4N_2$ requires C, 69·8; H, 5·8%). The last ester (0·5 g.) was added to a solution of potassium hydroxide (0·65 g.) in ethanol, (2 c.c.), and the whole refluxed for 8 hrs. The silver salt was precipitated from the resulting solution with silver nitrate and a little acetic acid. When it was heated in a vacuum, a pale yellow sublimate of 8-*lutidylquinoline* was obtained; recrystallised from light petroleum, it formed needles (100 mg.), m. p. 132° (Found: N, 12·0. $C_{16}H_{14}N_2$ requires N, 12·0%).

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110. *New Therapeutic Agents of the Quinoline Series. Part V. Pyridylacridines.*

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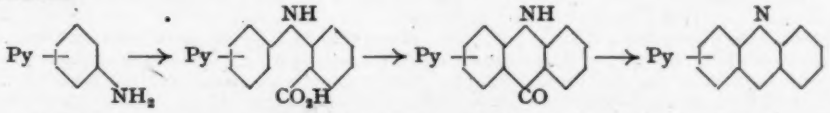
A series of pyridylacridines has been prepared for comparison with pyridylquinolines. Pyridylanilines of known orientation were condensed with *o*-chlorobenzoic acid, the products cyclised, and the resulting pyridylacridones reduced. Additional experiments on pyridyldiphenylamines and the preparation of 5-*β*-pyridylacridine from diphenylamine and nicotinic acid are also described.

In other papers of this series it has been shown not only that many pyridylquinolines possess spasmolytic activity but also that this property persists when the unsubstituted pyridyl nucleus is replaced by other heterocyclic systems. It was therefore desirable to see whether the quinoline nucleus also could be replaced by other basic groups. In the present work a number of compounds containing linked pyridine and acridine nuclei are described. The bactericidal and therapeutic qualities of acridines made this series of particular interest, but those members which were prepared proved to be much less active than the comparable pyridylquinolines.

The general method of preparation was to cyclise suitable pyridyldiphenylaminecarboxylic acids and reduce the resulting acridones:



Thus α-4-aminophenylpyridine was converted into 4-α-*pyridyldiphenylamine*-2′-*carboxylic acid* by heating in amyl alcohol with *o*-chlorobenzoic acid and potassium carbonate in presence of copper powder (cf. Tuttle, *J. Amer. Chem. Soc.*, 1923, **45**, 1906). This acid was converted into 3-α-*pyridylacridone* in almost theoretical yield by the action of sulphuric acid at 90°. Attempts to reduce this acridone to the acridine with zinc dust (Graebe and Lagodzinski, *Ber.*, 1892, **25**, 1735) or with potassium cyanide were unsuccessful, only oils being obtained. Sodium amalgam gave an impure product in low yield and the best results, though they were still not completely satisfactory, were obtained with aluminium amalgam in alcoholic solution.

In the course of this work 4-α-pyridyldiphenylamine-2′-carboxylic acid was decarboxylated to 4-α-*pyridyldiphenylamine*. This constitution was confirmed by allowing diazotised 4-aminodiphenylamine to react with pyridine, a good yield of 4-*pyridyldiphenylamines* being obtained; fractionation of the picrate of this material afforded only one of the anticipated three isomerides which proved to be identical with the above product of decarboxylation.

Reaction of β-4-aminophenylpyridine with *o*-chlorobenzoic acid afforded 4-β-*pyridyldiphenylamine*-2′-*carboxylic acid* and this was cyclised in good yield to the acridone, which was reduced, again best with aluminium

amalgam, to 3-β-*pyridylacridine*. A similar series of reactions was carried out with γ-4-aminophenylpyridine, leading to 3-γ-*pyridylacridine*, though this aniline was much less reactive towards *o*-chlorobenzoic acid and gave only a very poor yield of 4-γ-*pyridyldiphenylamine-2'-carboxylic acid*. In the same manner α-2-aminophenylpyridine was converted into 2-α-*pyridyldiphenylamine-2'-carboxylic acid*, which was smoothly cyclised to 1-α-*pyridylacridone* with hot sulphuric acid; reduction with aluminium amalgam then gave 1-α-*pyridylacridine*.

Finally the interaction of nicotinic acid and diphenylamine in presence of zinc chloride at 260° (cf. Bernthsen, *Annalen*, 1884, **224**, 1) gave a poor yield of 5-β-*pyridylacridine*. In this synthetic method, the yield of acridine obtainable from a carboxylic acid and diphenylamine is known to vary greatly and it was not surprising to find that picolinic acid failed to give any of the desired 5-α-pyridylacridine.

Representative pyridylanilines were condensed with *o*-chloronitrobenzene to give, for example, 2'-*nitro*-4-α-*pyridyldiphenylamine*; such compounds we hoped to cyclise to pyridylnitroacridines and thence by reduction, diazotisation and reaction with pyridine, to obtain dipyridylacridines. The poor yields in the Bernthsen synthesis and the unfavourable spasmolytic activity of monopyridylacridines already prepared caused this part of the project to be abandoned.

Experimental.

3-α-*Pyridylacridine*.—α-4-Aminophenylpyridine (m. p. 97°, 6 g.), *o*-chlorobenzoic acid (5·5 g.), potassium carbonate (6·5 g.), and copper bronze (0·2 g.) in amyl alcohol (60 c.c.) were refluxed for 3½ hours, the amyl alcohol then removed in steam, and the residual solution heated with charcoal for 1 hour, filtered, and made alkaline with ammonia. The 4-α-*pyridyldiphenylamine-2'-carboxylic acid* obtained crystallised from alcohol in yellow prisms (5·5 g.), m. p. 198° (Found: C, 74·8; H, 5·1. $C_{18}H_{14}O_2N_2$ requires C, 74·5; H, 4·8%). A solution of the acid (5 g.) in concentrated sulphuric acid (50 c.c.) was warmed on the steam-bath for 25 minutes and poured into water, and excess of ammonia added. Filtration gave 3-α-*pyridylacridone* (4·8 g.), which crystallised from alcohol in yellow needles, m. p. 315—317° (Found: C, 79·7; H, 4·5. $C_{18}H_{12}ON_2$ requires C, 79·4; H, 4·4%). Its solution in concentrated sulphuric acid was pale yellow with blue fluorescence, in alcoholic potassium hydroxide pale yellow with green fluorescence.

3-α-Pyridylacridone (3 g.) was dissolved in 95% alcohol (160 c.c.) containing sodium hydroxide (1·7 g.) and precipitated in a finely divided state by neutralisation with 5N-hydrochloric acid, amalgamated aluminium foil (1·25 g.) added during 2 hours with stirring and the whole refluxed until the aluminium had dissolved. The solution was filtered, the residue extracted with alcohol, and the combined liquors evaporated to dryness under reduced pressure. The product was extracted with hot hydrochloric acid (4N), and the extracts heated to boiling and treated with aqueous ferric chloride (10%) until a permanent excess was present. The solution was filtered and made alkaline, and the precipitate extracted with alcohol. After removal of alcohol the dark oil was extracted with benzene, and the solution concentrated to about 100 c.c., filtered, and chromatographed on a column of alumina (28 × 1·3 cm.); the lower pale yellow band was developed with benzene and eluted with benzene containing 10% of ether. Evaporation of the eluate gave 3-α-*pyridylacridine* (0·8 g.), which formed pale yellow needles, m. p. 140°, from benzene–light petroleum (Found: C, 84·2; H, 4·7. $C_{18}H_{12}N_2$ requires C, 84·2; H, 4·7%).

3-β-*Pyridylacridine*.—4-β-*Pyridyldiphenylamine-2'-carboxylic acid* was obtained from β-4-aminophenylpyridine, exactly as described for the α-isomeride, as a powder, which separated from ethanol in brownish needles, m. p. 248—250° (decomp.) (Found: N, 9·6. $C_{18}H_{14}O_2N_2$ requires N, 9·6%). 3-β-*Pyridylacridone*, prepared as above, crystallised from ethanol in yellow micro-needles, m. p. 314—316°. A dilute solution in alcohol had violet fluorescence, and a solution in concentrated sulphuric acid was yellow with blue fluorescence (Found: C, 79·1; H, 4·4%). Reduction of the acridone gave, after chromatography on alumina, the *acridine* (0·8 g.), which formed pale yellow needles, m. p. 132°, from light petroleum (Found: C, 84·3; H, 4·4%).

3-γ-*Pyridylacridine*.—γ-4-Aminophenylpyridine was converted as in the preceding examples into 4-γ-*pyridyldiphenylamine-2'-carboxylic acid*, which crystallised from ethanol in brown needles, m. p. 244° (Found: C, 74·1; H, 5·1%). The crude product was cyclised to give 3-γ-*pyridylacridone*, which separated from aqueous alcohol in pale yellow needles, m. p. 343° (Found: C, 79·4; H, 4·4%). In concentrated sulphuric acid the fluorescence was blue, in alcoholic potassium hydroxide green, and in dilute alcohol violet. The acridone (2 g.) was reduced as already described for the α-isomeride. Chromatography on alumina of the impure product in benzene solution gave 3-γ-*pyridylacridine* (0·25 g.), which crystallised from benzene in yellow leaflets, m. p. 179° (Found: C, 84·0, H, 4·9%).

1-α-*Pyridylacridine*.—From α-2-aminophenylpyridine (8 g.) and *o*-chlorobenzoic acid (7·8 g.), crude 2-α-*pyridyldiphenylamine-2'-carboxylic acid* (12·7 g.) was obtained. Crystallisation from benzene–light petroleum gave pale yellow prisms, m. p. 165—166° (Found: C, 75·1; H, 5·0%). Cyclisation of the acid, followed by crystallisation of the product from dilute ethanol, gave 1-α-*pyridylacridone* (9·5 g.) in yellow needles, m. p. 186—187°. The solution in alcoholic potassium hydroxide showed blue fluorescence (Found: C, 79·6; H, 4·4%). 1-α-Pyridylacridone (8 g.) was reduced overnight in boiling aqueous alcohol (95%, 400 c.c.) with amalgamated aluminium (4·5 g.). Oxidation of the crude product in dilute hydrochloric acid with ferric chloride and chromatography on alumina from benzene solution afforded 1-α-*pyridylacridine* (2 g.), which crystallised from benzene–light petroleum in yellow needles, m. p. 111·5°. Concentrated sulphuric acid gave a yellow solution with bright green fluorescence (Found: C, 84·2; H, 5·0%).

5-β-*Pyridylacridine*.—Nicotinic acid (5 g.), diphenylamine (7 g.), and finely powdered zinc chloride (15 g.) were heated at 260° for 14 hours, the product ground and dissolved in hot alcohol, and the extract evaporated to 100 c.c. and poured into excess of concentrated aqueous ammonia. The black tar was extracted with benzene, and the extracts washed with 2N-hydrochloric acid. Chromatography of the liberated base on alumina from benzene–ether, followed by distillation in a high vacuum at 140°, gave a yellow semi-solid product (*ca.* 1 g.) which on repeated crystallisation from benzene–light petroleum yielded yellow leaflets, m. p. 118° (Found: C, 84·4; H, 4·7%).

4-*Pyridyldiphenylamine*.—The paste obtained by rapidly cooling a solution of 4-aminodiphenylamine (20 g.) in warm 20% sulphuric acid (320 c.c.) to 5° was diazotised with sodium nitrite (7·8 g.). The mixture was kept overnight at 0°, and diphenylamine-4-diazonium sulphate then salted out with ammonium sulphate and added during 1 hour to pyridine (500 c.c.) stirred at room temperature. The solution was kept overnight, made alkaline, pyridine removed in steam, and the residue extracted with hot benzene. Washing, drying, and removal of solvent gave a black viscous oil, which was distilled at low pressure. 4-Pyridyldiphenylamine (7 g.), b. p. 220—235°/<1 mm., was obtained as a dark red oil. Conversion into the picrate and crystallisation from acetone gave a pure *picrate* (3 g.), m. p. 196·5° (Found: N, 14·55. $C_{17}H_{14}N_2,C_6H_3O_7N_3$ requires N, 14·7%). The picrate (2 g.) was heated on the steam-bath for 30 minutes with aqueous sodium hydroxide (5%, 100 c.c.), and the precipitated 4-pyridyldiphenylamine (*ca.* 1 g.) collected. Chromatographed in benzene solution on alumina, it formed a well-defined, narrow, yellow band below other coloured zones. Elution, with benzene containing 10% of ether gave a pure compound, regarded as 4-α-*pyridyldiphenylamine* (0·8 g.), m. p. 133°

which, recrystallised from benzene–light petroleum, formed pale yellow sheaves of needles, m. p. 133° (Found : C, 83·0; H, 5·8. $C_{17}H_{14}N_2$ requires C, 82·9; H, 5·7%).

4-α-Pyridyldiphenylamine-2′-carboxylic acid (5 g.) was heated with copper powder (0·3 g.) at 240° for 30 minutes. The product was extracted with hot benzene, and the extracts filtered, evaporated to small volume, and chromatographed on alumina. The lower, pale yellow band was developed with benzene and washed through the tower with benzene containing 10% of ether. 4-α-Pyridyldiphenylamine (4 g.) was recovered and recrystallised from benzene–light petroleum to yield 3·3 g., m. p. 134°; it gave no depression with the product previously described, m. p. 133°.

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111. *New Therapeutic Agents of the Quinoline Series. Part VI. Quinolyl-thiazoles, -amidines, and -pyrroles.*

By H. COATES, A. H. COOK, I. M. HEILBRON, and F. B. LEWIS.

Seven cyanoquinolines have been prepared and converted into thioamides; these in turn were condensed with bromoacetone (in one case, with bromoacetal) to yield thiazoles. Several of the nitriles were converted into amidines, but attempts to condense these with acetylacetone in order to obtain quinolylpyrimidines were unsuccessful. A number of *N*-pyrrylquinolines, obtained by condensing aminoquinolines with 1 : 4-dicarbonyl compounds, are also described.

As the spasmolytic activity of simple pyridylquinolines appeared also in comparable lutidylquinolines, it was thought advisable to prepare compounds containing a quinoline system linked to other simple heterocyclic nuclei. Recalling the similar biological activities of sulphapyridine and various sulphathiazoles, we selected the thiazylquinoline system for examination.

2-, 3-, 4-, and 5-Cyanoquinoline were prepared by slight modifications of the literature methods. As neither fusion of potassium quinoline-6-sulphonate with potassium cyanide (Fischer and Willmack, *Ber.*, 1884, **17**, 449) nor distillation of the diquinolylthiourea with paraffin and copper bronze (D.R.-P. 259,363) appeared convenient for the preparation of 6-cyanoquinoline, we obtained this compound in rather poor yield by a Sandmeyer reaction on 6-aminoquinoline. The same method afforded 8-cyano-6-methoxyquinoline; in this case the instability of the diazonium salt obtained from 8-amino-6-methoxyquinoline seemed to make neutralisation of acid as was done by Strukow (*Chem. pharmaz. Ind. Russ.*, 1934, **3**, 13; *Chem. Zentr.*, 1935, I, 2371) inadvisable. The usefulness of *Bz*-aminoquinolines in such reactions is surprisingly variable and we were, for example, unable to convert 6-amino-8-methoxyquinoline into the nitrile either by direct diazotisation or by using the nitrosoacetamido-compound. 8-Cyanoquinoline was obtained by distilling 8-chloroquinoline in presence of cuprous cyanide; a considerable quantity of the 8-amide was formed.

Each of these nitriles was converted into the corresponding thioamide by heating with alcoholic hydrogen sulphide, and thence by condensation with bromoacetone into the 5′-methyl-2-thiazylquinoline.

It appeared possible that the spamolytic activity of compounds of the pyridylquinoline type might be traced to the common feature of a basic residue separated from the quinoline nucleus by at least one carbon atom. Opportunity was therefore taken to convert some of the nitriles prepared above into iminoethers and thence into the corresponding amidines, which, however, as reported in Part I, proved to be inactive. Attempts to condense the amidines with acetylacetone in order to obtain quinolylpyrimidines were unsuccessful because of the unusually ready fission of the amidines into amides.

Of pyrrylquinolines, the 2 : 2′-representative had been prepared and Lions and his co-workers (*J. Proc. Roy. Soc. N.S. Wales*, 1936, **70**, 43; 1937, **71**, 92; 1940, **74**, 443) have described the preparation of *N*-5′-quinolyl-, -8′-quinolyl-, and -3′-quinaldyl-2 : 5-dimethylpyrrole by condensing appropriate aminoquinolines with acetonylacetone. In the present work this synthetic method was extended to the preparation of *N*-3′-quinolyl-, -6′-quinolyl-, -6′-methoxy-8′-quinolyl-, and -8′-methoxy-6′-quinolyl-2 : 5-dimethylpyrrole. In similar manner, by substituting diacetylsuccinic ester for acetonylacetone, a variety of quinolyldicarbethoxydimethylpyrroles was obtained. None of these new pyrrylquinolines had any appreciable spasmolytic activity.

EXPERIMENTAL.

2-5′-*Methyl-2′-thiazylquinoline.*—A solution of 2-cyanoquinoline (Hamer, J., 1939, 1011) (2 g.) in ethanol (15 c.c.) and concentrated aqueous ammonia (15 c.c.) was saturated with hydrogen sulphide and heated in a sealed tube at 150° for 4 hours. The *quinoline-2-thioamide* (1·3 g.) obtained crystallised from methanol in needles which were converted into prisms on standing, m. p. 168—169° (Found : N, 14·6. $C_{10}H_8N_2S$ requires N, 14·9%). A mixture of the thioamide (1·3 g.) and bromoacetone (1·5 c.c.) in ethanol (5 c.c.) was heated on the steam-bath for 1 hour and after removal of solvent the residue was treated with water (20 c.c.) and concentrated hydrochloric acid (10 c.c.), filtered, and neutralised. 2-5′-*Methyl-2′-thiazylquinoline*, recrystallised from aqueous ethanol, had m. p. 121·5—122·5°; yield, quantitative (Found : N, 12·5. $C_{13}H_{10}N_2S$ requires N, 12·4%).

3-5′-*Methyl-2′-thiazylquinoline.*—A mixture of 3-bromoquinoline (47 g.) and cuprous cyanide (29 g.) was heated gently until reaction commenced. From the reaction mixture, 3-cyanoquinoline was sublimed in a vacuum; recrystallised from benzene–light petroleum, it had m. p. 104° (yield, 10 g.). The nitrile was treated at 130° for 3 hours with ethanol and ammonium sulphide as above. *Quinoline-3-thioamide* formed pale yellow crystals from ethanol, m. p. 197—198° (decomp.) (Found : N, 14·9; S, 16·6. $C_{10}H_8N_2S$ requires N, 14·9; S, 17·0%). On heating with bromoacetone and ethanol as in the above example, 3-5′-*methyl-2′-thiazylquinoline* was obtained (yield, 0·8 g. from 2 g. of thioamide); it separated from benzene–light petroleum in rosettes of needles, m. p. 118—118·5° (Found : N, 12·3%).

4-5′-*Methyl-2′-thiazylquinoline.*—4-Cyanoquinoline (Kaufmann, *Ber.*, 1918, **51**, 121) (4 g.) in ethanol (25 c.c.) and

15% alcoholic ammonia (35 c.c.) saturated at 0° with hydrogen sulphide was heated at 120° for 3 hours. After removal of solvent and crystallisation of the residue from ethanol–light petroleum, *quinoline-4-thioamide* separated in pale yellow plates (2·3 g.), m. p. 223° (decomp.) (Found : N, 14·8%). A mixture of the thioamide (1·5 g.) and bromoacetone (1·5 g.) was warmed gently, and reaction completed with ethanol (6 c.c.) and bromoacetone (0·5 g.). The residue was dissolved in dilute hydrochloric acid, the filtered solution basified, and the solid distilled at 100—110° in a high vacuum. *4-5′-Methyl-2′-thiazylquinoline* (1·4 g.) was further purified by chromatography on alumina in benzene solution and finally crystallised from aqueous ethanol or benzene–light petroleum; it formed almost colourless prisms, m. p. 82·5—83·5° (Found : N, 12·4%).

5-5′-Methyl-2′-thiazylquinoline.—5-Cyanoquinoline (Fieser and Hershberg, *J. Amer. Chem. Soc.*, 1940, **62**, 1640) (2·0 g.) was dissolved in 20% alcoholic ammonia (45 c.c.) and aqueous ammonia (*d* 0·88, 5 c.c.), and the solution saturated with hydrogen sulphide at 0°. Heating at 120° for 3 hours and removal of solvent gave *quinoline-5-thioamide*, which separated from methanol in yellow prisms (1·2 g.), m. p. 187—188° (decomp.) (Found : S, 16·7%). The thioamide (1 g.) was condensed with bromoacetone (1 g.) in ethanol (5 c.c.) on the steam-bath. After removal of solvent, the residue was extracted with 15% hydrochloric acid, the solution made alkaline, and the precipitate chromatographed in benzene on alumina. *5-5′-Methyl-2′-thiazylquinoline*, recrystallised from aqueous methanol, formed fine colourless needles, m. p. 97—98° (Found : N, 12·4%).

6-5′-Methyl-2′-thiazylquinoline.—6-Aminoquinoline (19 g.), dissolved in concentrated sulphuric acid (41·5 c.c.) and water (76 c.c.), was diazotised at 0° with 15% sodium nitrite solution (64 c.c.). After 1 hour, the solution was added with vigorous stirring to excess of cuprous cyanide solution, and the reaction completed by keeping for 1 hour at 60°. Extraction of the red solid with benzene and crystallisation of extracted material from light petroleum gave 6-cyanoquinoline (5 g.), m. p. 131° (lit., 131—135°). The nitrile (1·1 g.) was dissolved in dry ethanol (10 c.c.), ethanol saturated with ammonia (20 c.c.) added, and the whole saturated with hydrogen sulphide at 0°. The semi-solid mass was heated for 1·5 hours under pressure at 100°, and solvent removed. The residual *quinoline-6-thioamide* crystallised from much water in buff needles, m. p. 184—185° (decomp.) (Found : N, 14·7%). The thioamide (0·5 g.) was condensed with bromoacetone (0·75 g.) in ethanol (3 c.c.), solvent removed, the product dissolved in dilute hydrochloric acid, and the solution basified. The brown oily deposit soon solidified and was purified by distillation at 90—100° in a high vacuum. *6-5′-Methyl-2′-thiazylquinoline* formed pale yellow clusters of prisms, m. p. 90·5—91·5°, from benzene–light petroleum (Found : N, 12·3%).

8-2′-Thiazylquinoline.—*o*-Chloroaniline (85 g.), sulphuric acid (*d* 1·56, 435 c.c.), sodium *m*-nitrobenzenesulphonate (192 g.), and glycerol (128 g.) were refluxed for 9 hours. The cooled solution was made alkaline with ammonia and distilled in steam. The distillate (18 l.) was extracted with benzene, and the extract dried and distilled, eventually in a vacuum. 8-Chloroquinoline (75 g.) was collected at 174°/25 mm. The chloro-compound was converted into 8-cyanoquinoline by Fieser and Hershberg's method (*loc. cit.*), quinoline-8-amide being obtained in considerable quantity as a by-product. *Quinoline-8-thioamide*, prepared as in previous similar reactions, separated from methanol–ether in yellow needles, m. p. 112—112·5° (decomp.); yield, 3 g. from 4 g. of nitrile (Found : N, 14·7%). A mixture of quinoline-2-thioamide (1 g.), bromoacetal (10 c.c.), and dilute sulphuric acid (3 c.c.) was heated on the steam-bath with intermittent shaking for 15 minutes in a closed flask. After being kept overnight, the product was extracted with 15% hydrochloric acid, the solution filtered and made alkaline, and the precipitate chromatographed on alumina from benzene. The material recovered from the filtrate was crystallised from benzene–light petroleum (yield, 0·7 g.). *8-2′-Thiazylquinoline* had m. p. 69—70° (Found : N, 13·3. $C_{12}H_8N_2S$ requires N, 13·2%).

Quinoline-2-amidine.—Dry hydrogen chloride was passed into a solution of 2-cyanoquinoline (2 g.) in dry ethanol (5 c.c.) and benzene (25 c.c.) cooled in ice. The precipitate which first appeared redissolved and the whole was kept for several days at 0°. The precipitate of quinoline-2-iminoether hydrochloride was ground with dry ether and with ethanol, added immediately to 15% alcoholic ammonia (40 c.c.), and shaken at room temperature for 4 days. Ammonium chloride was removed, the filtrate concentrated to small bulk, and the amidine hydrochloride precipitated with ether as an extremely hygroscopic solid. Its *picrate*, prepared from an alcoholic solution of the hydrochloride and picric acid, separated from acetone in yellow prisms, m. p. 258—259° (decomp.) (Found : N, 20·8. $C_{10}H_9N_3,C_6H_3O_7N_3$ requires N, 21·0%).

Quinoline-3-amidine.—Quinoline-3-iminoether hydrochloride was prepared from 3-cyanoquinoline as above. The precipitated hydrochloride was washed with dry ether and shaken with 15% alcoholic ammonia (50 c.c.) for 24 hours. Ammonium chloride was removed, the filtrate concentrated, and *quinoline-3-amidine hydrochloride* precipitated with dry ether; it separated from ethanol–ether in colourless prisms (3·5 g.), m. p. 168—169° (decomp.) after drying at 140—150° for 20 hrs. (Found : N, 20·0. $C_{10}H_9N_3,HCl$ requires N, 20·1%).

Quinoline-6-amidine.—6-Cyanoquinoline (2·2 g.) was converted into the corresponding amidine as in the foregoing reaction. *Quinoline-6-amidine hydrochloride* separated from ethanol–ether in colourless prisms (1 g.), m. p. 242° (decomp.) (Found : N, 19·8%).

Quinolyldicarbethoxydimethylpyrroles.—Ethyl diacetylsuccinate (4·5 g.) and the appropriate aminoquinoline (2·5 g.) were dissolved in ethanol (9 c.c.) and acetic acid (1 c.c.) and the whole boiled under reflux for 24 hours. The product was made alkaline with ammonia, water (50 c.c.) added, and the pyrrole extracted with benzene (20, 10 c.c.).

The combined extract was dried and filtered through a short column of alumina. On evaporating the filtrate, the pyrrole remaining slowly crystallised. *Ethyl 1-5′-quinolyl-2 : 5-dimethylpyrrole-3 : 4-dicarboxylate* separated from ether in stout prisms, m. p. 99° (yield, 50%) (Found : N, 7·7. $C_{21}H_{22}O_4N_2$ requires N, 7·7%). The corresponding *6′-quinolyl* compound had m. p. 115° (Found : N, 7·7%) and the corresponding *6′-methoxy-8′-quinolyl* and *8′-methoxy-6′-quinolyl* compounds separated from benzene–light petroleum in prisms, m. p. 141 and 117° respectively (Found : N, 7·3, 7·2 respectively. $C_{22}H_{24}O_6N_2$ requires N, 7·1%).

Quinolyldimethylpyrroles.—Acetonylacetone (2·0 g.) and the appropriate aminoquinoline (0·5 g.) were refluxed in ethanol (9 c.c.) and acetic acid (1 c.c.) for 24 hours, the solution poured into water (100 c.c.) containing ammonia in excess, and the precipitate collected and extracted with boiling light petroleum. When the extracts were concentrated and cooled, the pure quinolyldimethylpyrroles were obtained. The following were prepared : *1-3′-Quinolyl-2 : 5-dimethylpyrrole*, m. p. 167° (yield, 30%) (Found : N, 12·6. $C_{15}H_{14}N_2$ requires N, 12·6%); *1-6′-methoxy-8′-quinolyl-2 : 5-dimethylpyrrole*, m. p. 147° (yield, 23%) (Found : N, 11·0. $C_{16}H_{16}ON_2$ requires N, 11·1%).

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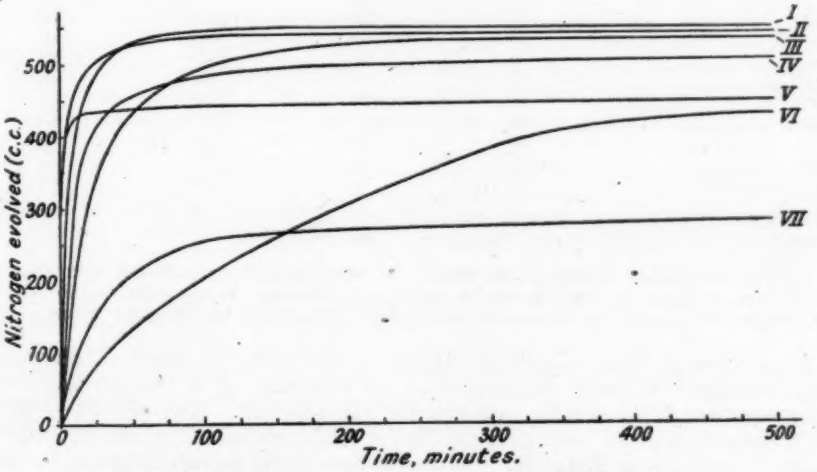
112. *Reactions of Hydrazoic Acid. Part II. A Quantitative Study of the Action with Substituted Benzoic Acids.*

By Lindsay H. Briggs and John W. Lyttleton.

A quantitative study has been made of the decomposition of hydrazoic acid alone and of its action upon a series of substituted benzoic acids (mostly *m*-substituted) in trichloroethylene solution in the presence of concentrated sulphuric acid at 40°. The rate of reaction of the substituted benzoic acids as determined by the time of half the evolution of nitrogen is, in general, in the reverse order of their strength as acids measured by the dissociation constants, with the exception of *o*-nitrobenzoic acid where an "ortho-effect" is observed. The total yield of nitrogen evolved and the yield of amine produced, however, do not bear any similar close relation: explanations for this are suggested. The mechanism of the Schmidt reaction is discussed.

Schmidt (*Ber.*, 1924, **57**, 704; D.R.-P., 1928, 500,435; *et al.*) found that hydrazoic acid reacts with benzoic acid in chloroform or benzene solution in the presence of concentrated sulphuric acid 40° to give an 85% yield of aniline, whereas ketones such as acetophenone (Schmidt, *loc. cit.*; Briggs and De Ath, J., 1937, 456) react under similar conditions, but usually at lower temperatures, to give good yields of the corresponding amide, acetophenone forming acetanilide. Oesterlin (*Angew. Chem.*, 1932, **45**, 536; cf. also Part I, J., 1942, 61) has extended this work to substituted benzoic acids and other acids and found that the substituents markedly affect the yield of amine produced.

We now report a quantitative study of the influence exerted by substituents on the replacement of the carboxyl group by the amino-group in the Schmidt reaction, intended to elucidate the mechanism of the reaction.



I. *Benzoic acid.*
II. o-*Nitrobenzoic acid.*
III. m-*Chlorobenzoic acid.*
IV. m-*Hydroxybenzoic acid.*
V. m-*Toluic acid.*
VI. m-*Nitrobenzoic acid.*
VII. *Hydrazoic acid.*

Schmidt (Knoll and Co. and Schmidt, E.P. 250,897, 23.9.25; Schmidt and Zutavern, B.P. 331,947, 19.4.29; Knoll A.-G. Chem. Fabr. and Schmidt, B.P. 430,774, 23.7.34) has recorded that other catalysts besides concentrated sulphuric acid, *e.g.*, phosphorus penta- or oxy-chloride, or ferric, aluminium, or stannic chloride, may act as catalysts in the reaction. We have found, however, that with phosphorus oxychloride as a catalyst in homogeneous solution in both chloroform and trichloroethylene, benzoic acid is converted into aniline by hydrazoic acid at 40° to the extent of only 5 and 6% respectively. The effect of substituents could also be obtained by using substituted acetophenones, and in a similar experiment with acetophenone, hydrazoic acid, and phosphorus oxychloride in chloroform solution, after 3—4 hours at 25° and a further hour at 40°, only 40% of acetanilide was obtained, 56% of the acetophenone being recovered unchanged. As both these results are unsatisfactory for a quantitative study, we have used concentrated sulphuric acid as the catalyst in heterogeneous solution but under standard conditions as set out in the experimental section. This method does not give completely satisfactory results owing to the initial rise in temperature on mixing the reagents.

Schmidt (*loc. cit.*) found that benzene and xylene react with hydrazoic acid in the presence of concentrated sulphuric acid at 60—70° to form aniline and xylidine respectively. To evaluate this phase of the reaction at 40°, typical compounds exerting strong *op*-directing influence (anisole and dimethylaniline) and strong *m*-directing influence (nitrobenzene) were submitted to the Schmidt reaction at 40°. In all cases, however, no trace of amine could be detected, nearly the whole of the starting materials being recovered unchanged. It would appear, therefore, that nuclear substitution does not occur to any appreciable extent at 40°.

We have now examined the Schmidt reaction on benzoic acid and fourteen substituted acids, choosing the

m-substituted acids for the main investigation, since a *m*-substituent exerts an influence almost exclusively by induction and only slightly and indirectly by a mesomeric effect. *o*- or *p*-Groups, however, have both types of effect, sometimes acting in opposite directions so that the activity on the nucleus is the algebraic sum of the two effects (Ingold, *Chem. Rev.*, **1934**, **15**, 231).

In our experiments we allowed 0·250 mol. of aromatic acid to react with 0·025 mol. of hydrazoic acid in trichloroethylene solution (100 c.c.) in the presence of concentrated sulphuric acid (0·15 mol.) at 40° under standard experimental conditions until all evolution of nitrogen had ceased. The gases evolved were passed through a soda–lime tower to absorb carbon dioxide, the remaining nitrogen being measured in a graduated burette over 50% potassium hydroxide solution. At the conclusion of the experiment the amount of amine formed and the unchanged acid were determined by direct isolation.

The experiments were repeated with *m*-toluic (extremely rapid), benzoic, and *m*-nitrobenzoic acids and were reproducible to within 5, 1, and <1%, respectively. A blank experiment with hydrazoic acid alone was also carried out. The results of these experiments are in the table, $t_{\frac{1}{2}}$ being the time of half-reaction, and typical curves of the rate of nitrogen evolution are in the figure.

Acid.	Yield of amine, %.	Acid recovered, %.	Vol. of N_2 at N.T.P. c.c.	Vol. of N_2 at N.T.P. %.	$t_{\frac{1}{2}}$, mins.
m-Chlorobenzoic	75	—	535	95·5	12
m-Bromobenzoic	72	—	515	92	10
m-Iodobenzoic	62	32	452	80	15
m-Hydroxybenzoic (a)	80	15	507	91	5
m-Methoxybenzoic	77	16	500	89	4
m-Ethoxybenzoic	73	23	494	88	4
m-Nitrobenzoic	63	32	432	77	100
m-Cyanobenzoic (b)	59	38	404	72	18
*iso*Phthalic (b)	57	40	447	80	17
m-Toluic	42	51	448	80	2
Benzoic	69	25	552	98	3
o-Methoxybenzoic	80	17	558	99	5
p-Methoxybenzoic	78	17	512	91	1½
o-Nitrobenzoic	68	26	541	96	2
p-Nitrobenzoic (c)	41	54	385	69	120
Hydrazoic	—	—	280	50	22

(a) The yield of amine was estimated from the recovered acid owing to the ready oxidation of the aminophenol.
(b) In these cases, the amine sulphate was not soluble in the sulphuric acid layer and separated as a sludge in the trichloroethylene layer.
(c) This acid was not completely soluble in the 100 c.c. of solvent and the conditions were therefore not standard.
m-Aminobenzoic acid has been omitted from the series since it would be immediately absorbed by the sulphuric acid and would therefore react under conditions not comparable with those for the other acids.

Mechanism of the Schmidt Reaction.—Before discussing the above results it is necessary to consider the mechanism of this reaction. Schmidt suggested that the essential part is the interaction of hydrazoic acid with concentrated sulphuric acid, with formation of the imino-radical: $HN_3 \rightleftharpoons N_2 + [HN<]$. When this radical reacts with benzene or water (indirectly), aniline or hydroxylamine is produced: $C_6H_6 + [HN<] \longrightarrow C_6H_5\cdot NH_2$; $H\cdot OH + [HN<] \longrightarrow NH_2\cdot OH$. Polymerisation of the radical, followed by disproportionation, gives hydrazine, another of the known products of the reaction: $4[HN<] \longrightarrow 2[HN{:}NH] \longrightarrow N_2 + H_2N\cdot NH_2$.

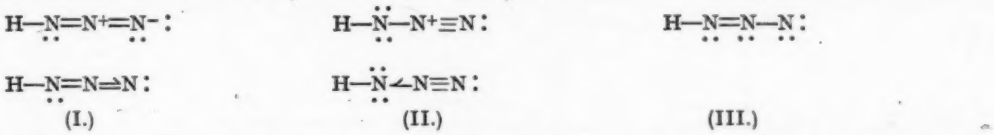
In the reaction with ketones and aldehydes addition of the imino-radical is assumed to form the oxime, which then undergoes the Beckmann rearrangement: $R\cdot CO\cdot R' + [HN<] \longrightarrow R\cdot C(:NOH)\cdot R' \longrightarrow R\cdot NH\cdot COR'$, the nitrile being formed if R′ = H. A similar process is considered to occur in the case of the carboxylic acids, the amine being formed from the carbamic acid produced as an intermediate: $R\cdot CO\cdot OH + [HN<] \longrightarrow R\cdot C(:NOH)\cdot OH \longrightarrow R\cdot NH\cdot CO_2H \longrightarrow R\cdot NH_2 + CO_2$.

Oliveri-Mandalà (*Atti R. Accad. Lincei*, **1910**, **19**, 228; *Gazzetta*, **1911**, **41**, i, 59; ii, 430; **1913**, **43**, i, 538, *et seq.*) criticised this mechanism (*ibid.*, **1925**, **55**, 271) and suggested that the initial step is probably the addition of hydrazoic acid to the carbonyl group to form the corresponding azide, which would then undergo decomposition to give the products obtained by Schmidt: $R\cdot CO\cdot R' + HN_3 \longrightarrow R\cdot CR'(OH)\cdot N_3 \longrightarrow R\cdot NH\cdot COR'$ or $R\cdot CO\cdot NHR'$.

There is strong evidence that Schmidt's mechanism is incorrect. If the imino-radical is concerned, the rate of the reaction should be controlled according to the rate of decomposition of hydrazoic acid. Schmidt found, however, that decomposition does not occur below 30°, and even at 60—70° it is not complete for 5 hours, whereas a number of ketones, *e.g.*, *cyclo*hexanone and benzylacetone, react vigorously at 0°. That the oxime is also not an intermediate as postulated by Schmidt is proved by the fact that the oxime of α-hydrindone is unchanged by heating with concentrated sulphuric acid at 100° (Kipping, J., **1894**, **65**, 480), whereas in the Schmidt reaction α-hydrindone is smoothly converted into hydrocarbostyril at 40° (Briggs and De Ath, *loc. cit.*).

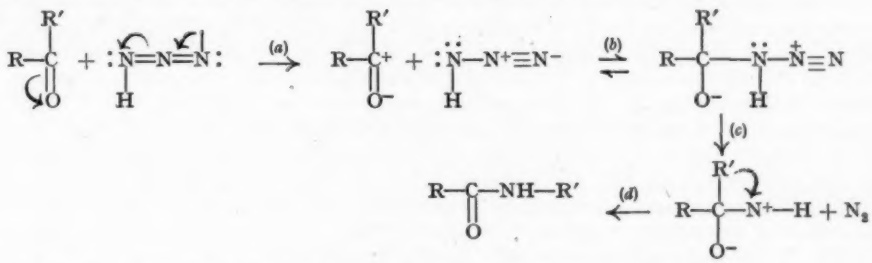
Recently, Hurd (Gilman, " Organic Chemistry : An Advanced Treatise," Vol. I, p. 699) has advanced a mechanism for the Schmidt reaction with which we agree, as it does not involve the imino-radical or the formation of an oxime as intermediate. It is based on the linear formulation of hydrazoic acid as a resonance hybrid

(cf. Hendricks and Pauling, *J. Amer. Chem. Soc.*, 1925, **47**, 2904; Sidgwick, *Trans. Faraday Soc.*, 1934, **30**, 801; Lindemann and Thiele, *Ber.*, 1928, **61**, 1529; Sidgwick, Sutton, and Thomas, J., 1933, 406), (I) being the



(I.) (II.) (III.)

stable and (II) and (III) the reactive forms. For our purposes we have considered the formula (II) as being that involved in the Schmidt reaction, which can then be formulated as follows :

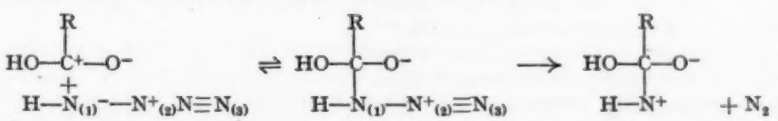


The first phase (*a*) is the activation of both the ketone or acid and hydrazoic acid under the influence of the strongly polar sulphuric acid, followed by addition (*b*) of the active hydrazoic acid molecule to the positive carbon of the carbonyl group. The addition complex loses nitrogen (*c*), and the remaining portion undergoes a further transformation (*d*) analogous to that postulated for the pinacol–pinacolone and allied transformations.

When R in the Schmidt reaction is an alkyl group, an amide is produced, but when R is OH (*i.e.*, in a carboxylic acid), a carbamic acid is formed which loses carbon dioxide spontaneously and yields the corresponding amine.

Discussion of Results.—A. *Rates of reaction.* If the time at which the reaction is half complete, as determined by the evolution of half the total volume of nitrogen, is considered to be a measure of the speed of the reaction, then by arranging the acids in descending order of speed, we have (*m*-series only) $CH_3 > H > O{\cdot}C_2H_5 > O{\cdot}CH_3 > OH > Br > Cl > I > CO_2H > CN > NO_2$, whereas acid strengths as measured by dissociation constants are nearly in the reverse order,* *viz.*, $NO_2 > CO_2H > CN > Br > Cl > I > OH > O{\cdot}CH_3 > O{\cdot}C_2H_5 > H > CH_3$. The Schmidt reaction is therefore of the same type as that of the decomposition of bromo-amides (Hauser and Renfrow, *J. Amer. Chem. Soc.*, 1937, **59**, 121) and the potassium salts of dihydroxamic acids (Renfrow and Hauser, *ibid.*, p. 2308; Bright and Hauser, *ibid.*, 1939, **61**, 618). In each case the speed of the reaction depends upon the character of the substituent, being slow or rapid according as this is electrophilic (*e.g.*, NO_2) or nucleophilic (*e.g.*, CH_3).

The phase representing the liberation of nitrogen involves the reaction :



In order to bring about the liberation of nitrogen in the second step, the charge on the nitrogen atom (2) must be neutralised by the transfer of an electron from the rest of the molecule to this atom. If R is nucleophilic, this step will occur rapidly and the rate of evolution of gas will be high; on the other hand, if R is electrophilic, the rate of nitrogen liberation will consequently be slow. In the case of the dissociation constants of the acids the converse argument will apply. An increased electron content of the carboxylic group caused by a nucleophilic substituent will repress the dissociation of the hydrogen as an ion, whereas withdrawal of electrons by an electrophilic group will enable ionisation to occur more readily. The inverted order of the acids with regard to their rates of reaction and dissociation constants is thereby explained.

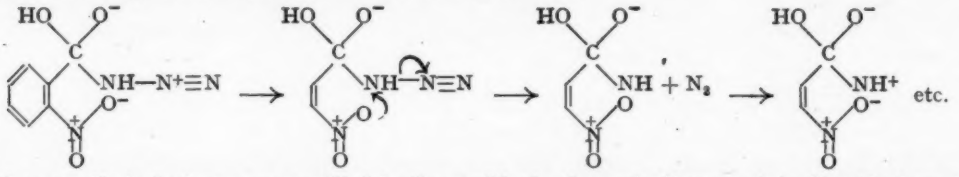
In our experiments the inversion of the bromo- and chloro-acids, and of cyanobenzoic and *iso*phthalic acid, with almost identical curves, may be due to experimental error, but the former type of inversion also occurred in the experiments of both Hauser and Renfrew (*loc. cit.*) and Bright and Hauser (*loc. cit.*).

In the series, *o*-, *m*-, and *p*-methoxybenzoic acids, there should be no chelation of the *o*-isomer. This is confirmed, the difference in the order of rates of reaction $p > m > o$ from that of the dissociation constants $p < o < m$ being possibly due to experimental error, since the values of the *o*- and *m*-acids are very close in both cases.

In the nitro-acid series a definite " ortho-effect " is observed. The *o*-acid, from its acid strength (the

* We are indebted to Mr. D. A. Tait, M.Sc., for measuring the dissociation constant of *m*-ethoxybenzoic acid, who obtained the value $6{\cdot}76 \times 10^{-5}$ by potentiometric titrations using the cell, Normal calomel electrode | Satd. KCl solution | 0·0025M-Acid solution + quinhydrone | Pt.

strongest in the series), should, according to the above considerations, react extremely slowly, whereas it reacts very rapidly—in our opinion, according to the following scheme :



It will be seen that electrons are supplied to the positively charged nitrogen atom directly from the nitro-group and not through the chain of carbon atoms. This process does not necessitate a high electron density drawn through the carbon atom from the nucleus, and is thus independent of the normal electrophilic character of the nitro-group in so far as it deactivates the nucleus and hence the side chain. Indeed, this very withdrawal of electrons from the nucleus makes them more directly available to the nitrogen atom by a process of chelation, the co-ordinate link providing the electrons where they are expressly needed.

This result also shows a similarity to those obtained by Hauser and Renfrow (*loc. cit.*) on the decomposition of bromobenzamides. The *o*-nitro-compound, according to the strength of the corresponding acid, should react more slowly than the *m*- and the *p*-compound, but it was found to react more rapidly, although the magnitude of the divergence was not nearly as large as that observed in this investigation. Moreover, whereas the decomposition of other substituted bromo-amides gave good constants corresponding to a reaction of the first order, yet for all three nitro-compounds application of the equation for a first-order reaction gave a " constant " varying over a range of 18—65%. A completely analogous mechanism may be envisaged also for the apparently anomalous decomposition of *o*-nitrobromobenzamide.

B. *Total yield of nitrogen and amine.* When the acids are arranged in order of the amount of nitrogen evolved and amine produced, different orders are obtained from those derived from the rates of reaction, although individual groups retain the same relative order, *viz.*, *m*-series, $Cl > Br > I$; $OH > OCH_3 > OC_2H_5$, $CO_2H > NO_2 > CN$ ($NO_2 > CN > CO_2H$ in the yield of amine), $H > CH_3$; methoxy-series, $o > p > m$; nitro-series, $o > m > p$. Consideration of the mechanism, however, provides a possible explanation.

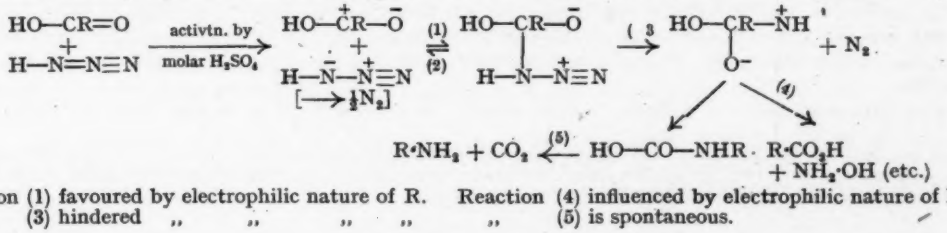
It must first be noticed that in the reaction with benzoic acid almost exactly 1 mol. of nitrogen is evolved, whereas hydrazoic acid alone under the same experimental conditions yields exactly ½ mol. Substituents on the benene nucleus, depending on their nucleophilic or electrophilic character, will affect the phases (*b*), (*c*), and (*d*) of the reaction in different ways.

In phase (*b*) an electrophilic group R′ affects the equilibrium in a forward direction by increasing the positive charge on the carbon atom and hence its readiness to undergo addition. Less free hydrazoic acid will thus decompose by itself and more through the Schmidt reaction, leading to relatively greater evolution of nitrogen and amount of amine formed. Where R′ is nucleophilic the reverse will hold. With *m*-nitrobenzoic acid the gas evolution is even much slower than that of hydrazoic acid itself, and it is obvious that the latter acid must be largely combined with the nitro-acid and not free to decompose by itself.

On the other hand, in phase (*c*) where R′ is electrophilic the reaction rate as already discussed is retarded, thus allowing any free hydrazoic acid a better chance to decompose by itself, and so leading to relatively lower evolution of nitrogen and amounts of amine formed.

If this were the complete explanation, a quantitative correlation should exist between the yields of nitrogen and amine, but this is not found. Since in some cases, such as benzoic acid itself, almost the theoretical amount of nitrogen is evolved but 25% of the acid is recovered, an alternative mechanism to phase (*d*) must occur, leading to regeneration of acid without affecting the nitrogen yield, and we suggest the following reaction with simultaneous formation of hydroxylamine or aminosulphuric acid, although there is so far no supporting experimental evidence : $R{\cdot}C\bar{O}(OH){\cdot}\overset{+}{N}H + H_2O$ (from H_2SO_4) $\longrightarrow R{\cdot}CO_2H + NH_2{\cdot}OH$ or $NH_2{\cdot}O{\cdot}SO_3H$. Where the substituent R is electrophilic, the aromatic nucleus is relatively more positively charged and there should be less tendency for it to migrate to the positively charged nitrogen and greater tendency for it to decompose by the alternative reaction. With the notable exception of toluic and benzoic acids, this is, in general, confirmed experimentally. A similar phenomenon is exemplified in Hauser and Renfrow's experiments; here, also, decomposition of substituted bromo-amides yields as main product the amine, as in the Schmidt reaction, as well as the corresponding acid. In their experiments the greater the electrophilic character of the substituent the greater was the yield of the corresponding acid up to 46% in the case of *m*-nitrobromobenzamide.

In conclusion, we may represent the mechanism of the Schmidt reaction with acids as follows :



Reaction (1) favoured by electrophilic nature of R. Reaction (4) influenced by electrophilic nature of R.
„ (3) hindered „ „ „ „ „ (5) is spontaneous.

The rate of the phase controlling the evolution of nitrogen can be correlated with other data such as the dissociation constant, but opposing effects of unknown magnitude prevent any such correlation in respect to the yield of amine and total nitrogen.

Experimental.

The apparatus used throughout consisted of a three-necked flask immersed in a small thermostat maintained at 40° ± 0·5°, one neck being fitted with a dropping funnel, the central neck with a mercury-sealed stirrer of the Witt type driven directly at constant speed, and the other neck connected first through a small reflux condenser and then through a soda–lime tower to gas burettes. The gas burettes containing 50% potassium hydroxide solution were interconnected and of two sizes, a larger one being used to measure the first rapid evolution of gas and the second to measure subsequent slower evolution. Water of constant temperature was run through both the reflux condenser and the jacket of the gas burettes.

The aromatic acid (0·025 mol.) was dissolved in the solution of hydrazoic acid (0·025 mol.) in freshly purified trichloroethylene, and the solution made up to 100 c.c. with this solvent. This solution was placed in the three-necked flask and allowed to reach 40°, 8 c.c. of concentrated sulphuric acid (previously warmed to 40°) then being run in through the tap-funnel. Stirring was now commenced, and the evolution of nitrogen measured in either of the two gas burettes according to the rate of reaction. The reaction was continued until the rate of evolution did not exceed 1 c.c. in 15 minutes, the volume of nitrogen evolved being corrected to N.T.P.

At the conclusion of the reaction, the trichloroethylene layer was removed by suction, and any unchanged acid recovered as such in the ordinary way. The sulphuric acid layer was diluted with 250 c.c. of water (including washings), and any amine sulphate produced filtered off and weighed as such. The filtrate was freed from traces of trichloroethylene by gravity filtration and made alkaline with ammonia. If the amine was solid, it was filtered off and weighed as such together with further amounts formed after concentration, but if it was liquid, it was recovered by extraction with ether and removal of the ether after drying, first by distillation and finally by passing a current of dry air over the residue until the weight of amine was constant. All liquid amines were identified by the preparation of a solid derivative, usually benzoyl or acetyl. In no case was there any divergence in the identity of the amine from that expected from the substituted acid.

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Auckland University College, Auckland, New Zealand. [*Received, April 20th*, 1942.]

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113. *The Influence of Alkylation on the Reactions of Acid Derivatives in the Friedel–Crafts Synthesis.*

By Eugene Rothstein and M. A. Saboor.

When acids or their chlorides or anhydrides are treated under various conditions with reagents such as phosphoric oxide and anhydrous aluminium chloride, their reactions fall into two classes. The first, which includes mainly the primary and secondary acid derivatives, yields ketones (under Friedel–Crafts conditions) or ketones and carbon dioxide (Kipping, J., 1890, **57**, 532); in the second, tertiary acids always eliminate carbon monoxide and the product is an unsaturated substance or its polymeride (cf. *inter alia* Laughlin and Whitmore, *J. Amer. Chem. Soc.*, 1932, **57**, 532). In the present paper these reactions are discussed and a mechanism which explains them is suggested. Experiments have been carried out which fully confirm the hypotheses put forward, and a new application of the Friedel–Crafts synthesis is described, whereby tertiary acid anhydrides or chlorides lose carbon monoxide with replacement of a carboxyl group by an aromatic nucleus. This reaction affords an improvement on the method devised by Whitmore and his collaborators for diagnosing tertiary aliphatic acids.

Much of the work on the Friedel–Crafts synthesis deals with the function of the catalyst, comparatively little attention having been directed to the influence of substituents; the present investigation deals with the influence of alkyl groups on the course of the reaction when acid derivatives are treated with aluminium chloride or other substances having a similar catalytic action.

I. When alkylated succinic anhydrides are treated with benzene and aluminium chloride, the phenyl group tends to attach itself to the carbonyl group next to the least alkylated carbon atom (compare *inter alia*, Mayer and Stamm, *Ber.*, 1923, **56**, 1424; Haworth, J., 1932, 1128; Clemo and Dickenson, J., 1937, 255; Desai and Wali, *Proc. Indian Acad. Sci.*, 1937, **6***A*, 135). Methylsuccinic anhydride, for instance, yields a mixture of β-benzoyl-β- (I) and -α-methylpropionic acid* (II), the second being the major product. Desai and Wali (*loc. cit.*), using phenylsuccinic anhydride and toluene, isolated five times as much β-toluoyl-α-phenyl- (III) as

(I.) $COPh\cdot CHMe\cdot CH_2\cdot CO_2H$ $COPh\cdot CH_2\cdot CHMe\cdot CO_2H$ (II.)

(III.) $C_6H_4Me\cdot CO\cdot CH_2\cdot CHPh\cdot CO_2H$ $C_6H_4Me\cdot CO\cdot CHPh\cdot CH_2\cdot CO_2H$ (IV.)

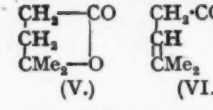
β-toluoyl-β-phenyl-propionic acid (IV) when toluene was also the solvent, but in nitrobenzene the proportions were reversed. Both Haworth (*loc. cit.*) and Desai and Wali advance similar mechanisms which ascribe the preferential formation of (I) to the repulsion of the phenyl anion by the inductive effect of the alkyl groups. The latter authors further regard the preponderating amount of one or other of the isomerides (III) or (IV) as due to the ability of the phenyl group to act both as an electron source and as an electron sink. This, however, is not acceptable since, among other reasons, a similar explanation cannot be applied to methylsuccinic anhydride. The effect of nitrobenzene may be significant in view of its high ionising power (see below), and in this connection Desai and Wali report that when *gem*-dialkyl groups or ring structures such as *cyclo*-pentane or

* In order to simplify comparison, in all appropriate cases the substances are regarded as derivatives of propionic acid, but systematic names also are given for new compounds.

-hexane substitute one of the methylene groups of succinic anhydride, *e.g.*, in *cyclo*pentane-1-carboxylic-1-acetic anhydride, the product is always the β-benzoyl-α-substituted propionic acid, $COPh\cdot CH_2\cdot C(:C_4H_8)\cdot CO_2H$, even in nitrobenzene solution. It is known that phenyl *tert.*-alkyl ketones, $Ph\cdot CO\cdot CR_3$, cannot be prepared by the Friedel–Crafts reaction, but are usually obtained by alkylation of the phenyl dialkyl ketone (Haller and Bauer, *Compt. rend.*, 1909, **148**, 72). Reasons for this are discussed later.

II. Kipping (J., 1890, **57**, 532, 980; 1893, **63**, 452) found that fatty acids ranging from *n*-heptoic to stearic yielded ketones when heated with excess of phosphoric oxide at 180—220°, carbon dioxide being eliminated. More recently, Laughlin and Whitmore (*J. Amer. Chem. Soc.*, 1932, **54**, 4462) and Whitmore and Crooks (*ibid.*, 1938, **60**, 2078) analysed the gases evolved when various alkylated fatty acids mixed with phosphoric oxide were heated to 155—160°. The experiments showed that primary and secondary acids yielded small quantities of carbon dioxide containing a small proportion of monoxide, but with tertiary acids such as trimethyl-, dimethylethyl-, methyldiethyl-, and methyl-*tert.*-butyl*neo*pentyl-acetic acids, the yields of carbon monoxide increased with increasing alkylation, being 55% for the first and over 90% of the theoretical for the last. Very small amounts of carbon dioxide (corresponding, presumably, to ketone formation) were also formed, but the yield never exceeded 0·6%, whereas under the same conditions for less alkylated acids the quantity was of the order of 6%. The residues were usually tars, but those from trimethylacetic acid were mainly polymerised *iso*butylene.

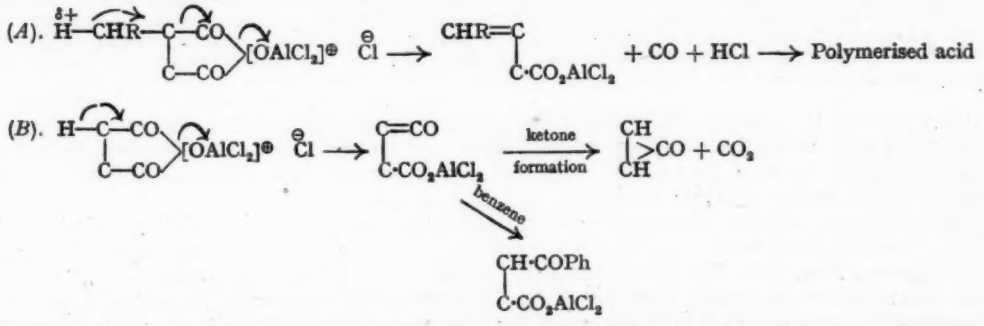
III. The reactions between aluminium chloride and acid chlorides and anhydrides have also in certain cases been found to lead to elimination of carbon monoxide; *e.g.*, *as*-dimethylsuccinic anhydride affords ββ-dimethylacrylic acid, $CMe_2{:}CH\cdot CO_2H$, and carbon monoxide when warmed with aluminium chloride in chloroform solution (Desfontaines, *Compt. rend.*, 1902, **134**, 295), and similarly αα-dimethylglutaric anhydride yields the lactone of γ-hydroxy-γ-methylvaleric acid (V) and γ-methyl-Δ^{β}-pentenoic acid (VI) with loss of carbon monoxide, the lactone obviously being derived from the unsaturated acid by subsequent hydration. This reaction does not take place with α-methylglutaric anhydride.



(V.) (VI.)

Two final instances of analogous reactions of importance in this connection are the formation of carbon monoxide, hydrogen chloride, and a polymerised hydrocarbon when trimethylacetyl chloride is mixed with aluminium chloride at 0°, and of carbon monoxide, hydrogen chloride, and *iso*butylenedisulphonic acid when the same substance is heated with concentrated sulphuric acid at 100° (Boëseken, *Rec. Trav. chim.*, 1910, **29**, 100).

In all the above examples it is evident that the absence of an *ionisable* α-hydrogen atom leads to formation of an unsaturated substance, usually polymerised, with loss of carbon monoxide; in other cases little of the latter is eliminated and a ketone results, and in this connection the reactions of dimethylsuccinic anhydride in the non-ionising chloroform solution may be of significance. The possible mechanisms for these reactions are outlined in (*A*) and (*B*) in which aluminium chloride is depicted as the catalyst. The corresponding reactions with other catalysts are probably essentially similar.



The interpretation (*A*) of the experiments of Whitmore and his collaborators is further illustrated in the present paper by the dry distillation of calcium β-phenyl-ααββ-tetramethylpropionate (as XI), which furnishes an unsaturated hydrocarbon with loss of carbon monoxide and water, no ketone being formed. The keten-like intermediate in (*B*) may represent a transition structure only and not a definite compound. It is envisaged that reaction with acid chlorides is precisely similar, with analogous mechanisms. This is of some importance because, though the literature does not reveal a case of cyclic ketone formation from an anhydride and aluminium chloride, diethyl ketone and di-*n*-propyl ketone are produced when propionyl and *n*-butyryl chlorides, respectively, are treated with anhydrous ferric chloride (Hamonet, *Bull. Soc. chim.*, 1888, **50**, 355).*

Two other deductions may be drawn from the above formulation of these related reactions, and we have obtained experimental confirmation for both of them.

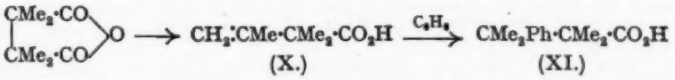
(1) The normal reaction of acid derivatives with aluminium chloride and benzene is only possible where an

* The course of the final stage in (*B*) does not affect the arguments advanced in this paper, but the probable intermediate formation of a propiopropionyl chloride–ferric chloride complex in the formation of ketones from acid chlorides suggests an analogy with the Claisen reaction.

α-hydrogen atom is present, and in this case the aromatic nucleus will attach itself to the carbonyl group nearest to the one which is most ionised. This is again shown in that the sole product from trimethylsuccinic anhydride is β-*benzoyl-ααβ-trimethylpropionic acid* [β-*benzoyl-αα-dimethyl*-n-*butyric acid*], $COPh\cdot CHMe\cdot CMe_2\cdot CO_2H$ (VII). The structure assigned to this acid follows from its identity with the acid obtained by methylation of β-benzoyl-αα-dimethylpropionic acid, $COPh\cdot CH_2\cdot CMe_2\cdot CO_2H$ (VIII). This acid, m. p. 173° (Clemo and Dickenson; Desai and Wali), whose structure was not previously completely established, has now been directly compared with the isomeric β-benzoyl-ββ-dimethylpropionic acid, $COPh\cdot CMe_2\cdot CH_2\cdot CO_2H$ (IX), m. p. 101°, synthesised from sodio*iso*butyrophenone and ethyl iodoacetate (Haller and Ramart-Lucas, *Compt. rend.*, 1914, **159**, 143). Direct comparison of (VII) with β-benzoyl-αββ-trimethylpropionic acid, $COPh\cdot CMe_2\cdot CHMe\cdot CO_2H$, was not possible because the latter could not be prepared: attempted syntheses from sodio*iso*butyrophenone and methyl α-iodopropionate, or from (IX) by alkylation were both unsuccessful. On the other hand, alkylation of β-*benzoyl-αβ-dimethylpropionic acid* [β-*benzoyl-α-methyl*-n-*butyric acid*], $COPh\cdot CHMe\cdot CHMe\cdot CO_2H$, afforded (VII).

(2) As a corollary of (1), it should not be possible to obtain a ketone or a ketonic acid by the Friedel–Crafts reaction on the anhydrides or acid chlorides of tertiary acids. In these cases, the unsaturated acid first formed may be expected to condense with benzene to give β-phenyl derivatives. Experiments carried out both with tetramethylsuccinic and with trimethylacetic anhydride succeeded in illustrating this. A third experiment shows that the postulated intermediate compound (X) in (*A*) reacts in the expected manner.

When tetramethylsuccinic anhydride was condensed with benzene in the presence of aluminium chloride, carbon monoxide was immediately evolved in 60% yield in the cold. The main product (yield at least 70%) was β-*phenyl-ααββ-tetramethylpropionic acid* [β-*phenyl-ααβ-trimethyl*-n-*butyric acid*] (XI). The *methyl* ester was identical with that obtained when the methyl ester of (X) (Courtot, *Bull. Soc. chim.*, 1906, **35**, 298) was



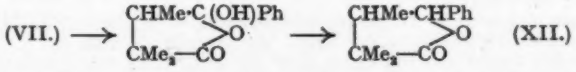
treated with benzene and aluminium chloride. Hydrolysis furnished the acid, identical with (XI). Though both β-*chloro*- and β-hydroxy-ααββ-tetramethylpropionic esters similarly yield (XI), its structure is not without ambiguity.. The possible isomeric β-benzyl-ααβ-trimethylpropionic acid, $CH_2Ph\cdot CHMe\cdot CMe_2\cdot CO_2H$, has not been prepared and the independent synthesis of (XI) was found impracticable. The next lower homologue, methyl αα-dimethyl-β-methylenepropionate, $CH_2{:}CH\cdot CMe_2\cdot CO_2Me$, however, does afford an acid which is probably β-*phenyl-ααβ-trimethylpropionic acid* [β-*phenyl-αα-dimethyl*-n-*butyric acid*], $CHPhMe\cdot CMe_2\cdot CO_2H$, since its m. p. differs from that of β-benzyl-αα-dimethylpropionic acid obtained by the reduction of (VIII).

Exactly similar results to the foregoing were obtained with trimethylacetic anhydride: trimethylacetic acid, *tert.*-butylbenzene (yield, 55%), and carbon monoxide were isolated: $(CMe_3\cdot CO)_2O + C_6H_6 \longrightarrow CPhMe_3 + CMe_3\cdot CO_2H + CO$.

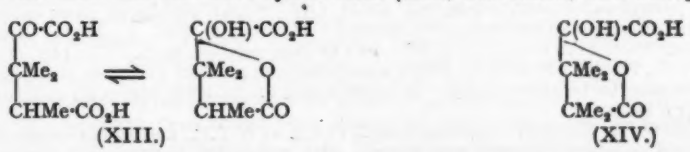
Whitmore's work was designed to obtain a suitable method for distinguishing tertiary from primary and secondary acids, but it would appear that the action of aluminium chloride on a benzene solution of the acid chloride or anhydride is a simpler test, since in all cases carbon monoxide is eliminated at room temperature and there is the added advantage that the use of phosphoric oxide is avoided.

Two more points need elaborating. Attempts were made to synthesise the acid (IX) by a Friedel–Crafts reaction on the half ester chloride, $COCl\cdot CMe_2\cdot CH_2\cdot CO_2Me$, but only the isomeride (VIII) was isolated, although the corresponding methyl ketone, $COMe\cdot CMe_2\cdot CH_2\cdot CO_2Me$ has been prepared from this substance (Blanc, *Bull. Soc. chim.*, 1901, **25**, 68), but by the Grignard reaction. The acid (XI) is similarly the only product obtained from the half ester chloride of tetramethylsuccinic acid.

Both β-benzoyl-αα-dimethylpropionic acid (VIII) and its ester yield ketonic derivatives, and the former is reduced to β-benzyl-αα-dimethylpropionic acid. On the other hand, no ketonic reactions could be obtained



from the methylated homologue (VII), and on reduction the lactone of γ-hydroxy-γ-phenyl-ααβ-trimethylbutyric acid (XII) was formed. Comparison with α-keto-ββγ-trimethylglutaric acid (XIII), which exists as a tautomeric mixture of the keto- and the keto-cyclol form (Kon, Stevenson, and Thorpe, J., 1922, **121**, 654;



Rothstein, Stevenson, and Thorpe, *ibid.*, 1925, **127**, 1073), and with α-keto-ββγγ-tetramethylglutaric acid (XIV), which is stable only in the keto-cyclol form (Rothstein and Shoppee, J., 1927, 531), suggests that the terminal methyl group has a greater influence in conferring stability on the ring structure than has the β-methyl group.

EXPERIMENTAL.

Derivatives of β-Benzoyl-αα-dimethylpropionic Acid (VIII).—The acid was prepared in 80% yield from *as*-dimethylsuccinic anhydride (17 g.), benzene (70 g.), and aluminium chloride (36 g.), and after decolorisation (charcoal) separated from ethyl acetate in prisms, m. p. 173° (Found: C, 69·6; H, 6·5. Calc.: C, 69·9; H, 6·8%). When titrated with potassium hydroxide it gave a sharp end-point with phenolphthalein and was reprecipitated by carbon dioxide. A solution of the acid in concentrated sulphuric acid was yellow, and on warming, the colour changed to orange, then dark blood-red. The 2 : 4-*dinitrophenylhydrazone* separated from absolute alcohol in yellow plates, m. p. 198—199° (Found: C, 55·5; H, 4·6; N, 14·4. $C_{18}H_{18}O_6N_4$ requires C, 55·9; H, 4·7; N, 14·5%). The *methyl* ester, b. p. 153°/7 mm., was prepared (i) in 85% yield by saturating a solution of the acid in twice the theoretical quantity of methyl alcohol with dry hydrogen chloride, or (ii) from the silver salt and methyl iodide; it separated from petrol (b. p. 60—80°) in plates, m. p. 46—47° (Found: C, 70·2; H, 6·9. $C_{13}H_{16}O_3$ requires C, 70·9; H, 7·3%), and furnished a 2 : 4-*dinitrophenylhydrazone* which crystallised from absolute alcohol in orange leaflets, m. p. 126° (Found: C, 56·6; H, 5·0; N, 13·6. $C_{19}H_{20}O_6N_4$ requires C, 57·0; H, 5·0; N, 14·0%).

Action of acetyl chloride. When the acid (VIII) was refluxed with excess of acetyl chloride, hydrogen chloride was evolved, and after removal of the solvent, the residual *γ-phenyl-αα-dimethyl-Δβ-butyrolactone* was crystallised from petrol (b. p. 40—60°), and had m. p. 45° (Found: C, 76·0; H, 6·4. $C_{12}H_{12}O_2$ requires C, 76·6; H, 6·4%).

Reduction with hydriodic acid. The acid was reduced by refluxing it with excess of hydriodic acid (*d* 1·9) for 5 hours in glacial acetic acid containing a little red phosphorus. The β-benzyl-αα-dimethylpropionic acid so obtained had been previously prepared by Clemo and Dickenson (*loc. cit.*) by reduction with amalgamated zinc (Found: C, 75·0; H, 8·3. Calc.: C, 75·0; H, 8·3%).

Alkylation. Methyl β-benzoyl-αα-dimethylpropionate (5·6 g.) was added to a boiling solution of potassium (1·6 g.) in *tert.*-butyl alcohol. The mixture was boiled for a further 20 minutes, cooled somewhat, and methyl iodide (10 c.c.) added, the refluxing being continued until the solution was neutral. The product after isolation and hydrolysis with alcoholic potash afforded β-benzoyl-*aaβ*-trimethylpropionic acid (VII) in 80% yield. It was identical (m. p. and mixed m. p.) with that described below.

Derivatives of β-Benzoyl-αβ-dimethylpropionic Acid.—Aluminium chloride (70 g.) was gradually added to *trans*-αβ-dimethylsuccinic anhydride (43 g.) dissolved in dry benzene (250 c.c.). A fairly brisk reaction took place and the liquid boiled gently. After 15 hours, the mixture was warmed at 100° for a short time, decomposed with ice and sulphuric acid, and extracted with ether. The dried extract furnished *β-benzoyl-αβ-dimethylpropionic acid* [*β-benzoyl-α-methyl*-n-*butyric acid*], which crystallised from petrol (b. p. 60—80°) in needles, m. p. 78—79°; yield 59 g., 86% (Found: C, 69·3; H, 6·0. $C_{12}H_{14}O_3$ requires C, 69·9; H, 6·8%). This acid, unlike β-benzoyl-αα-dimethyl-, -ββ-dimethyl-, and -*aaβ*-trimethylpropionic acids, (VIII), (IX), and (VII), respectively, decomposed cold sodium bicarbonate solution easily. Its *methyl* ester, b. p. 164°/14 mm., was obtained in 89% yield in the same way as the αα-dimethyl ester (Found: C, 71·0; H, 7·3. $C_{13}H_{16}O_3$ requires C, 70·9; H, 7·3%).

Alkylation. A solution of the methyl ester (17 g.) in *tert.*-butyl alcohol (45 c.c.) containing potassium (3·1 g.) was refluxed with excess methyl iodide. The resulting liquid was freed from precipitated potassium iodide by centrifuging, and fractionally distilled. Analysis showed that the methylated ester, b. p. 168°/16 mm., still contained traces of the alcohol (Found: C, 73·6; H, 7·5. Calc.: C, 71·8; H, 7·7%). It was hydrolysed by 4 hrs.' refluxing with twice the calculated quantity of alcoholic potash, the solvent distilled off, and the residue dissolved in water. After extraction of the neutral compounds with ether, the aqueous layer was acidified with 7N-sulphuric acid, and the liberated oil extracted with ether. The acid (yield, 68·5% overall) crystallised after isolation and was identical with the trimethyl acid (VII) above (Found: C, 70·5; H, 7·3. Calc.: C, 70·9; H, 7·3%). Further alkylation could not be achieved by the same method, nor was it possible to alkylate either the dimethyl or the trimethyl acid by the use of sodamide in benzene (Haller and Bauer, *loc. cit.*).

Derivatives of β-Benzoyl-aaβ-trimethylpropionic Acid (VII).—Trimethylsuccinic anhydride (47·3 g.) when condensed with benzene (235 c.c.) and aluminium chloride (85 g.) afforded *β-benzoyl-aaβ-trimethylpropionic acid* [*β-benzoyl-αα-dimethyl*-n-*butyric acid*] (VII) (or *γ-hydroxy-γ-phenyl-aaβ-trimethylbutyrolactone*) separating from ethyl acetate in clusters of needles, m. p. 135·6°. Yield, 55% (Found: C, 70·9; H, 7·2. $C_{13}H_{16}O_3$ requires C, 70·9; H, 7·3%). In a second experiment a crude yield of 85% was obtained from the anhydride mixed with twice its weight of aluminium chloride and five times its weight of benzene.

The substance was a weak acid and its potassium salt was decomposed by carbon dioxide. A yellow solution in concentrated sulphuric acid became orange on standing and a deep permanganate colour on gentle warming. When added to water, the product formed a blue solution and sulphur dioxide was evolved. The *methyl* ester (or *ether*) was obtained by the usual method in 89% yield; b. p. 151°/8 mm. (Found: C, 71·6; H, 7·9; $C_{14}H_{18}O_3$ requires C, 71·8; H, 7·7%). Neither the acid nor the ester yielded a ketonic derivative. The acid was converted into *γ-phenyl-aaβ-trimethyl-Δβ-butyrolactone*, b. p. 145°/10 mm., when it was refluxed with excess of acetyl chloride (Found: C, 77·6; H, 6·8. $C_{13}H_{14}O_2$ requires C, 77·2; H, 6·9%). Reduction of the acid with hydriodic acid gave *γ-phenyl-aaβ-trimethylbutyrolactone* (XII), crystallising from petrol (b. p. 40—60°) in short needles, m. p. 71° (Found: C, 76·2; H, 7·8. $C_{13}H_{16}O_2$ requires C, 76·5; H, 7·8%).

Reaction between Tetramethylsuccinic Anhydride and Benzene.—The anhydride (20 g.) was dissolved in dry benzene contained in a flask connected to a gas-jar over water. Aluminium chloride (25 g.) was added gradually with shaking and ice-cooling, and after the liquid had remained at 0° for some time, the temperature was gradually raised to 100° and maintained there until the evolution of gas, which had been fairly brisk at the commencement of the reaction, had ceased. The product was decomposed by ice, the benzene distilled, and the residue treated with excess of hydrochloric acid. After filtration, the substance was dissolved in sodium hydroxide solution, and the small amount of neutral product (about 0·1 g. after crystallisation) filtered off. Acidification of the alkaline solution afforded *β-phenyl-aaββ-tetramethylpropionic acid* [*β-phenyl-aaβ-trimethyl*-n-*butyric acid*], (XI), which separated from alcohol or ethyl acetate in needles, m. p. 179°. Yield of recrystallised acid, 70% (Found: C, 75·6; H, 8·8. $C_{13}H_{18}O_2$ requires C, 75·7; H, 8·8%). The neutral *substance* crystallised from petrol (b. p. 60—80°) in long needles, m. p. 147—148° (Found: C, 81·7; H, 7·9. $C_{30}H_{32}O_2$ requires C, 81·6; H, 7·5%). Evidently it was a condensation product with two phenyl groups, but the quantity was too small for its structure to be determined. It crystallised unchanged, however, from boiling alcoholic potash and so was not an ester or a lactone.

The volume of gas collected in the above reaction was 2170 c.c. at N.T.P., and the presence of carbon monoxide was established (blue flame). A measured volume was washed with potassium hydroxide, bromine water, and potassium hydroxide again, then finally with water, and absorbed in ammoniacal cuprous chloride. The total volume of carbon monoxide at N.T.P. thus measured was 1727 c.c., *i.e.*, 60% of the amount derivable from one carboxyl group.

β-p-Tolyl-aaββ-tetramethylpropionic [*-aaβ-trimethyl*-n-*butyric*] *acid*, similarly obtained by use of toluene instead of benzene, crystallised from ethyl acetate in needles, m. p. 178° (Found: C, 76·3; H, 9·0. $C_{14}H_{20}O_2$ requires C, 76·4; H, 9·1%).

Like the potassium salts of the highly alkylated benzoylpropionic acids, potassium β-phenyl-aaββ-tetramethylpropionate is decomposed by carbon dioxide with precipitation of the original acid. The silver and the calcium salt can be obtained by addition of silver nitrate and calcium chloride respectively to solutions of the potassium salt. Dry distillation of the calcium salt yielded an unsaturated *hydrocarbon*, $C_{13}H_{16}$, b. p. 110° (Found : C, 90·4; H, 9·6. $C_{13}H_{16}$ requires C, 90·0; H, 10·0%). A second *hydrocarbon* with the same empirical formula but b. p. 154° is obtained when the phenyltetramethylpropionic acid is distilled from its mixture with soda–lime (Found : C, 89·8; H, 10·1; *M*, 133. $C_{13}H_{16}$ requires C, 90·0; H, 10·0%; *M*, 160). Bromine was rapidly absorbed by both these hydrocarbons, yielding exceedingly lachrymatory bromo-derivatives.

Methyl β-phenyl-aaββ-tetramethylpropionate [*β-phenyl-aaβ-trimethyl*-n-*butyrate*], b. p. 138°/12 mm., was prepared in nearly theoretical yield from the silver salt and methyl iodide. It had a characteristic camphoraceous odour and separated from petrol (b. p. 40—60°) in leafy plates, m. p. 24—25° (Found : C, 76·8; H, 9·4. $C_{14}H_{20}O_2$ requires C, 76·4; H, 9·1%).

β-Phenyl-aaββ-tetramethylpropionic [*β-Phenyl-aaβ-trimethyl*-n-*butyric*] *anhydride* resulted from boiling the acid with acetic anhydride. It separated from petrol (b. p. 60—80°) in small plates, m. p. 87° (Found : C, 79·6; H, 8·7; *M*, 366. $C_{26}H_{34}O_3$ requires, C, 79·2; H, 8·6%; *M*, 394). A *mononitro*-derivative of the acid was prepared by heating it with excess of concentrated nitric acid on the steam-bath for 6 hours and diluting the product with water. It crystallised from ethyl acetate–petrol (b. p. 60—80°) in faintly yellow needles, m. p. 232° (Found : C, 62·5; H, 6·6; N, 5·9; *M*, 281. $C_{13}H_{17}O_4N$ requires C, 62·2; H, 6·8; N, 5·6%; *M*, 251).

2 : 2 : 3 : 3-*Tetramethyl-α-hydrindone* was formed by dissolving the tetramethyl acid in concentrated sulphuric acid. There was a slight evolution of heat, and after warming the liquid for a few minutes, it was diluted with water and extracted with ether. This afforded in quantitative yield a highly refracting, mobile liquid, b. p. 142°/25 mm. (Found : C, 83·2; H, 8·6; *M*, 181. $C_{13}H_{16}O$ requires C, 83·0; H, 8·5%; *M*, 188). It was also obtained in small yield by the prolonged heating of the acid with concentrated hydriodic acid and red phosphorus. The tetramethylhydrindone has a camphoraceous odour and is very resistant to the attack of reagents; the usual ketonic reactions are absent, and when it was heated on the steam-bath for 3 days with concentrated nitric acid, the oily layer gradually disappeared and dilution with water yielded a *nitro*-2 : 2 : 3 : 3-*tetramethyl-α-hydrindone*, separating from petrol (b. p. 60—80°) in faint yellow needles, m. p. 130—131° (Found : C, 67·6; H, 6·1; N, 6·3; *M*, 239. $C_{13}H_{15}O_3N$ requires C, 67·0; H, 6·4; N, 6·0%; *M*, 233).

Preparation of β-Phenylpropionic Acid Derivatives.—Methyl β-phenyl-aaβ-trimethylpropionate [*β-phenyl-aa-dimethyl*-n-*butyrate*] was obtained in 65% yield by the action of benzene (25 c.c.) and aluminium chloride (7 g.) on methyl dimethylvinylacetate (5 g.) prepared by Courtot's method (*Bull. Soc. chim.*, 1906, **35**, 118). The impure ester had b. p. 124—126° (Found : C, 74·8; H, 8·7. $C_{13}H_{18}O_2$ requires C, 75·7; H, 8·8%). Hydrolysis with alcoholic potash yielded the *acid*, separating from petrol (b. p. 40—60°), in which it was extremely soluble, in plates, m. p. 54—57° (Found : C, 74·5; H, 8·7. $C_{12}H_{16}O_2$ requires C, 75·0; H, 8·3%). The acid did not react with sodium bicarbonate solution.

Preparation of β-Phenyl-aaββ-tetramethylpropionic Acid (XI) *from Methyl aaβ-Trimethyl-β-methylenepropionate* (*as* X).—The ester (10 g.), dissolved in dry benzene (50 c.c.), was mixed with aluminium chloride (13 g.), and the reaction completed by heating the dark solution for ½ hr. Decomposition with ice and sulphuric acid, followed by extraction with ether, afforded a 78·5% yield of methyl β-phenyl-aaββ-tetramethylpropionate identical (m. p. and mixed m. p.) with that obtained from tetramethylsuccinic anhydride. Hydrolysis yielded the acid (XI), m. p. 179°. Similarly, ethyl β-hydroxy- and β-chloro-aaββ-tetramethylpropionate both furnished *ethyl β-phenyl-aaββ-tetramethylpropionate* [*β-phenyl-aaββ-trimethyl*-n-*butyrate*], b. p. 138°/11 mm. (Found : C, 76·2; H, 9·2; *M*, 211. $C_{15}H_{22}O_2$ requires C, 76·9; H, 9·4%; *M*, 234). Hydrolysis gave the acid, m. p. 179° (Found : C, 75·4; H, 8·6%; *M*, 237. Calc. : *M*, 206).

The conversion of ethyl β-hydroxy-aaββ-tetramethylpropionate into the chloro-derivative was a matter of some difficulty since phosphorus halides and thionyl chloride led mainly to the dehydration product, but the following method was effective. The hydroxy-ester (15 g.) was mixed with an equivalent amount of pyridine and thionyl chloride (10·4 g.) added, and the crystalline mass so obtained kept overnight, mixed with water, and extracted with ether. The dried extract was repeatedly fractionally distilled. The lower-boiling fraction (3·4 g.) was mainly unsaturated ester, but this could not be entirely separated from the *chloro*-ester, b. p. 70—74°/8 mm.; yield, 6·8 g., 41% (Found : C, 56·8; H, 9·0; Cl, 17·2; *M*, 205. $C_9H_{17}O_2Cl$ requires C, 56·1; H, 8·8; Cl, 18·4%; *M*, 192·5).

Reaction between Trimethylacetic Anhydride, Benzene, and Aluminium Chloride.—The anhydride was best prepared (yield 80%) by heating equivalent quantities of the acid chloride and the fused potassium salt at 100°. The yield was slightly increased by use of the dried silver salt instead of the potassium one and by extracting the anhydride from the reaction mixture with petrol. Trimethylacetic anhydride (12 g.) was slowly added to a mixture of benzene (50 c.c.) and aluminium chloride (12 g.). Carbon monoxide was immediately liberated, followed appreciably later by hydrogen chloride. The reaction was completed on the steam-bath, and the products isolated in the usual way. Trimethylacetic acid (yield, 8 g., *i.e.*, 63·5% of the total recoverable acid) (Found : C, 58·8; H, 10·2. Calc. : C, 58·8; H, 9·8%) was removed from the mixture by extraction with sodium hydroxide, and the *tert.*-butylbenzene (b. p. 59—61°/14 mm.) extracted with ether; yield, 4·8 g., 55·5% (Found : C, 89·4; H, 10·6; *M*, 141. Calc. : C, 89·6; H, 10·4%; *M*, 134). In a second experiment, the volume of carbon monoxide at N.T.P. eliminated from trimethylacetic anhydride (4·9 g.), benzene (21 g.), and aluminium chloride (7 g.) was 499 c.c. = 84·5%.

Experiments with β-Benzoyl-ββ-dimethylpropionic Acid (IX).—This acid, prepared from the ethyl ester (obtained in 21% yield from *iso*butyrophenone, sodamide, and ethyl iodoacetate), did not crystallise well and was therefore converted into its *methyl* ester (b. p. 131—143°/8 mm.) by saturating its solution in methyl alcohol with hydrogen chloride (Found : C, 70·4; H, 7·5. $C_{13}H_{16}O_3$ requires C, 70·9; H, 7·3%). Hydrolysis of this afforded the crystalline acid, m. p. 100—102° (Found : C, 69·5; H, 6·4. Calc. : C, 69·9; H, 6·8%). The m. p. was depressed when it was mixed with the isomeric β-benzoyl-aa-dimethylpropionic acid (VIII). It was recovered unchanged when its methyl ester was refluxed with potassium *tert.*-butoxide and excess of methyl iodide.

Attempted Synthesis of β-Benzoyl-aββ-trimethylpropionic Acid.—The following condensations were unsuccessful, in most cases the original reactants being recovered unchanged : bromo*iso*butyrophenone with ethyl methylsodiomalonate or with ethyl sodiocyanoacetate; sodio*iso*butyrophenone (prepared in benzene, by use of sodamide) or the potassio-compound (from potassium *tert.*-butoxide) with ethyl bromomalonate. The product of the reaction between ethyl α-iodopropionate and potassio*iso*butyrophenone was an ester of indeterminate b. p.; the acid obtained by hydrolysis did not crystallise and was therefore re-esterified with methyl alcohol. The resulting *methyl* ester, b. p. 95°/0·3 mm. (Found : C, 71·7; H, 7·8. $C_{14}H_{18}O_3$ requires C, 71·8; H, 7·7%), was possibly the required product, but a non-crystalline acid was again formed from it.

Most of the analyses were carried out by Drs. G. Weiler and F. B. Strauss of Oxford.

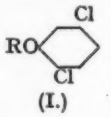
THE UNIVERSITY, LEEDS. [*Received, May 28th*, 1943.]

114. *The Halogenation of Phenolic Ethers and Anilides. Part XIV. m-Substituted Phenyl Ethers.*

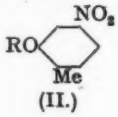
By Brynmor Jones.

Velocity coefficients for the chlorination of aromatic ethers of the type *m*-$C_6H_4X\cdot OR$, and for certain disubstituted ethers, where chlorination can occur simultaneously in more than one position, are recorded. Although the reactions are composite in character, it is found that the relative directive powers of OR groups obtained from a ratio of velocity coefficients are very similar to those found in ethers of the type *p*-$C_6H_4X\cdot OR$, where chlorination results in the formation of a single homogeneous product.

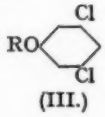
The series of ethers examined are of the type *m*-$C_6H_4X\cdot OR$, where X = NO_2, CO_2H, Cl, or F, and the types (I), (II), and (III). In each measurement an excess of ether was employed, the usual expression for a bimolecular reaction giving satisfactory velocity coefficients in all cases. The mean values are in Table I. The medium is again "the 99% acetic acid containing 1 c.c. of water per 100 c.c. of acetic acid," the concentrations are in g.-mol./l., and the time in minutes.



(I.)



(II.)



(III.)

Table I.

Velocity coefficients for the chlorination of compounds in 99% acetic acid, at 20°.

Type *m*-RO·$C_6H_4\cdot CO_2H$: $[Cl_2] = 0.0075$; [HCl] = 0.0375.

Concn. of ether	0·0225	0·0150		0·0225	0·0150		0·0225	0·0150
Mol. ratio, [ether]/[Cl_2]	3	2		3	2		3	2
R =	*k*.		R =	*k*.		R =	*k*.	
CH_3	1·63	1·67	C_6H_{13}[a]	—	3·54	$[CH_2]_2Ph$	2·01	2·08
C_2H_5	3·24	3·31	C_7H_{15}[a]	—	3·45	$[CH_2]_3Ph$	2·75	2·81
C_3H_7[a]	3·48	—	C_8H_{17}[a]	—	3·49	*p*-$C_6H_4F\cdot CH_2$	0·909	0·950
C_3H_7[β]	6·37	6·37	C_9H_{19}[a]	—	3·45	*p*-$C_6H_4Cl\cdot CH_2$	—	0·722
C_4H_9[a]	3·56	3·66	$C_{12}H_{25}$[a]	—	3·38	*p*-$C_6H_4Br\cdot CH_2$	—	0·692
C_5H_{11}[a]	3·40	3·55	$CH_2\cdot Ph$	1·14	—			

Type *m*-$C_6H_4X\cdot OR$: $[Cl_2] = 0.02$; [ether] = 0·10; [HCl] = 0·0475.

X =	R =	*k* × 10³.	X =	R =	*k* × 10³.
NO_2	CH_3	0·534	NO_2	C_2H_5	1·06

$[Cl_2] = 0.0075$; [ether] = 0·0075; [HCl] = 0·0375.

Cl	CH_3	75·8	F	*o*-$C_6H_4(NO_2)\cdot CH_2$	52·7
,,	CH_2Ph	52·7			

Type (I): $[Cl_2] = 0.0075$; [HCl] = 0·0375.

Concn. of ether	0·0225	0·0150		0·0225	0·0150
Mol. ratio, [ether]/[Cl_2]	3	2		3	2
R =	*k*.		R =	*k*.	
CH_2Ph	0·320	0·336	*p*-$C_6H_4Br\cdot CH_2$	0·189	—
p-$C_6H_4Me\cdot CH_2$	—	0·458	*m*-$C_6H_4F\cdot CH_2$	—	0·172
p-$C_6H_4F\cdot CH_2$	0·246	0·256			

Type (II): $[Cl_2] = 0.02$; [ether] = 0·10; [HCl] = 0·0475.

R =	*k* × 10².	R =	*k* × 10².	R =	*k* × 10².
CH_3	1·23	C_2H_5	2·44	CH_2Ph	0·834

Type (III): $[Cl_2] = 0.0075$; [HCl] = 0·0375.

Concn. of ether	0·0225	0·0075		0·0225	0·0075
Mol. ratio, [ether]/[Cl_2]	3	1		3	1
R =	*k*.		R =	*k*.	
CH_3	8·15	8·48	*p*-$C_6H_4Br\cdot CH_2$	3·70	3·83

For a complete understanding of any electrophilic benzene substitution reaction, knowledge is required of the total velocity of substitution and of the relative rates of reaction at the individual reactive centres, the latter being obtained usually from an analysis of the proportions of the isomerides formed. In the kinetic studies of the nuclear chlorination of aromatic ethers so far reported, the necessity of obtaining data for the proportions of isomerides did not arise, since in the great majority of ethers only one product is formed and the velocity coefficient is itself a direct measure of the reactivity at a particular carbon atom. In the present series this is no longer the case; *e.g.*, 2 : 5-dichlorophenyl ethers have two, and the *m*-alkoxybenzoic acids

three, reactive centres in the molecule, and a measure of their separate contributions to the reactivity as well as the total velocity of chlorination becomes essential. Interruption of this work makes it impossible to complete the present investigation by a study of the proportions, and it seems desirable therefore to place on record the data so far obtained and the tentative conclusions arising therefrom.

The interpretation of the results for compounds such as *m*-alkoxybenzoic acids where, in theory, three positions are available for substitution is simplified to a certain extent by the fact that, in practice, only two isomerides are formed. Holleman and his co-workers (" Die direkte Einführung von Substituenten in den Benzolkern," Leipzig, 1910) have shown that *m*-chlorobenzoic acid on nitration gives the 6- and the 2-nitro-3-chlorobenzoic acid in the ratio 93 : 7, and that *m*-bromobenzoic acid gives 89% and 11% respectively of the corresponding bromonitrobenzoic acids. Similarly, Beyer (*Rec. Trav. chim.*, 1921, **40**, 621) found that the chlorination of *m*-hydroxybenzoic acid in glacial acetic acid yields the 6-chloro- and the 2-chloro-3-hydroxybenzoic acids [see also Mazzara (*Gazzetta*, 1899, **29**, i, 376), who obtained the same two acids by the action of sulphuryl chloride]. An accurate estimation of the relative amounts of the two chlorohydroxybenzoic acids was not made, but it is clear from Beyer's work that the 6-chloro-acid is the chief product, with the 2-chloro-acid forming approximately 30% of the total. An approximate analysis carried out in the present work indicates that in the chlorination of *m*-methoxybenzoic acid the 6-chloro-3-methoxybenzoic acid is the chief product.

Further light is thrown on the significance of the present data by the demonstration by Miss Mabel L. Hemming, employing the method reported in J., 1936, 1231, that in the chlorination of anisole, phenetole, and certain substituted phenyl benzyl ethers in acetic acid the *o*/*p* ratio is almost unaltered by changes in the OR group. This result suggests that in the above *m*-substituted phenyl ethers changes in the alkoxy-group would probably not alter to any appreciable degree the relative reactivity at the 2- and the 6-position, and at the 4- and the 6-position in such ethers as those of 2 : 5-dichlorophenol. If this is so, then a general correspondence would be expected between the relative directive powers of OR groups in the present series of compounds and those recorded in earlier papers for compounds of the simpler type *p*-$C_6H_4X{\cdot}OR$ where only one product is formed. The velocity ratios in Table II show this correspondence.

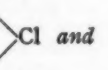
TABLE II.

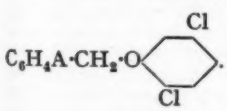
Relative directive powers of the groups OR *in compounds of the types* m- *and* p-$RO{\cdot}C_6H_4{\cdot}CO_2H$.

Values of $100k^{OR}_{CO_2H}/k^{OMe}_{CO_2H}$.

R =	CH_3.	C_2H_5.	$C_3H_7{}^a$.	$C_3H_7{}^\beta$.	$C_4H_9{}^a$.	$C_5H_{11}{}^a$.	$C_6H_{13}{}^a$.	$C_7H_{15}{}^a$.	$C_8H_{17}{}^a$.	$C_9H_{19}{}^a$.	$C_{12}H_{25}{}^a$.
m-CO_2H	100	198	214	382	219	211	212	207	209	207	202
p-CO_2H	100	198	215	444	221	218	216	213	207	203	202

R =	CH_2Ph.	$[CH_2]_2Ph$.	$[CH_2]_3Ph$.	*p*-$C_6H_4F{\cdot}CH_2$.	*p*-$C_6H_4Cl{\cdot}CH_2$.	*p*-$C_6H_4Br{\cdot}CH_2$.
m-CO_2H	70	124	169	56	43	41
p-CO_2H	70	119	171	59	45	44

Relative directive powers of the groups $C_6H_4A{\cdot}CH_2{\cdot}O$ *in compounds of the types* $C_6H_4A{\cdot}CH_2{\cdot}O$–  *and*



Values of $100k^{OCH_2{\cdot}C_6H_4A}_X/k^{OCH_2Ph}_X$.

A =	H.	*p*-Me.	*p*-F.	*p*-Br.	*m*-F.
p-Chloro-series	100	138	81	58	47
2 : 5-Dichloro-series	100	136	77	59	51

Comparison of the velocity coefficients in Table III shows that the deactivating substituents F, Cl, CO_2H, and NO_2 exert a smaller effect in the *m*- than in the *p*-position on the overall rate of chlorination, the influence of position being most noticeable in the case of fluorine and least noticeable in that of the strongly polar nitro-group.

TABLE III.

Substituent :	H.	F.	Cl.	CO_2H.	NO_2.
k, *m*-substituted anisole	*ca.* 900	*ca.* 380	76·0	1·60	0·0053
k, *p*- " "	*ca.* 900	2·32	1·23	0·444	0·0029

The effect of both number and position of chlorine atoms is exemplified by the comparison of *o*-, *m*-, and *p*-chloroanisoles and 2 : 4-, 2 : 5-, and 3 : 5-dichloroanisoles, for which the velocity coefficients are respectively, 4·44, 76·0, 1·23, 0·0031, 0·46, and 8·15.

EXPERIMENTAL.

The measurements of the velocity coefficients of chlorination were carried out at 20° as usual. The procedure of crystallising each ether at least three times from ethyl alcohol, glacial acetic acid, or, in some cases, from benzene was followed, and the satisfactory nature of the velocity coefficients when the ether : chlorine ratio was 3 : 1 or 2 : 1 is illustrated by the data in Table IV.

TABLE IV.

m-Methoxybenzoic acid.

[ether] = 0·0225; [Cl_2] = 0·0075; [HCl] = 0·0375.						[ether] = 0·0150; [Cl_2] = 0·0075; [HCl] = 0·0375.					
Time, mins.	Titre, c.c.	*k*.	Time, mins.	Titre, c.c.	*k*.	Time, mins.	Titre, c.c.	*k*.	Time, mins.	Titre, c.c.	*k*.
0	7·50	—	24·35	3·42	1·60	0	7·50	—	42·60	3·12	1·67
13·00	4·85	1·60	30·00	2·88	1·62	22·20	4·57	1·67		Mean	1·67
17·68	4·16	1·62		Mean	1·61	32·10	3·79	1·66			

m-*n*-Butoxybenzoic acid.

[ether] = 0·0225; [Cl_2] = 0·0075; [HCl] = 0·0375.						[ether] = 0·0150; [Cl_2] = 0·0075; [HCl] = 0·0375.					
0	7·50	—	8·917	3·90	3·58	0	7·50	—	15·68	3·62	3·65
5·433	4·93	3·65	12·33	3·12	3·58	10·13	4·56	3·68	19·10	3·16	3·66
				Mean	3·60					Mean	3·66

2 : 5-Dichlorophenyl benzyl ether.

[ether] = 0·0150; [Cl_2] = 0·0075; [HCl] = 0·0375.						[ether] = 0·0150; [Cl_2] = 0·0075; [HCl] = 0·0375.					
0	7·50	—	72·35	5·37	0·335	96·80	4·83	0·336	132·2	4·18	0·337
										Mean	0·336

Materials.—The analyses marked by an asterisk were carried out by the author; the remainder were micro-determinations by Dr. Ing. A. Schoeller or Messrs. Weiler and Strauss.

m-*Alkoxybenzoic acids.* These were prepared from *m*-hydroxybenzoic acid by the method employed earlier for the preparation of the isomeric *p*-alkoxybenzoic acids (J., 1935, 1834, 1874). Pure specimens were assured by crystallising each acid three times from glacial acetic acid. Three of the acids, the methoxy-, ethoxy-, and *n*-propoxy-, m. p.'s 104—105°, 137°, and 71—72°, respectively, had been prepared by Cohen and Dudley (J., 1910, **97**, 1737) by alkylation of the hydroxy-ester and subsequent hydrolysis. The present method is more economical since it does not involve the formation, and consequent hydrolysis, of the esters. The methoxy-, ethoxy-, and *n*-propoxy-benzoic acids crystallised from glacial acetic acid in long colourless prisms, m. p. 105°, m. p. 137° (Found: * C, 64·7; H, 6·1. Calc.: C, 65·1; H, 6·1%), and m. p. 74°, respectively. The iso*propoxybenzoic acid*, m. p. 96° (Found: * C, 66·5; H, 6·4. $C_{10}H_{12}O_3$ requires C, 66·7; H, 6·7%), and the n-*butoxybenzoic acid*, m. p. 62° (Found: * C, 68·1; H, 7·0. $C_{11}H_{14}O_3$ requires C, 68·0; H, 7·3%), crystallised similarly. The n-*amyloxybenzoic acid* crystallised from glacial acetic acid in clusters of colourless, elongated prisms, m. p. 72° (Found: * C, 69·6; H, 7·6. $C_{12}H_{16}O_3$ requires C, 69·2; H, 7·8%). From the same solvent, the n-*hexyloxybenzoic acid*, m. p. 71° (Found: * C, 70·5; H, 8·0. $C_{13}H_{18}O_3$ requires C, 70·3; H, 8·2%), the n-*heptyloxybenzoic acid*, m. p. 80° (Found: * C, 71·0; H, 8·3. $C_{14}H_{20}O_3$ requires C, 71·1; H, 8·5%), the n-*octyloxybenzoic acid*, m. p. 73° (Found: * C, 72·0; H, 8·5. $C_{15}H_{22}O_3$ requires C, 71·9; H, 8·9%), and the n-*nonyloxybenzoic acid*, m. p. 84° (Found: * C, 72·9; H, 9·0. $C_{16}H_{24}O_3$ requires C, 72·7; H, 9·2%), crystallised in clusters of colourless plates. The n-*dodecyloxybenzoic acid* had m. p. 91° (Found: * C, 74·8; H, 9·8. $C_{19}H_{30}O_3$ requires C, 74·5; H, 9·9%).

m-*Benzyloxybenzoic acid* crystallised from glacial acetic acid in clusters of colourless prisms, m. p. 134° (Found: * C, 73·5; H, 5·1. $C_{14}H_{12}O_3$ requires C, 73·7; H, 5·3%), whereas m-(p'-*fluorobenzyloxy*)*benzoic acid*, m. p. 148° (Found: C, 68·05; H, 4·4. $C_{14}H_{11}O_3F$ requires C, 68·0; H, 4·5%), the p'-*chloro-acid*, m. p. 170° (Found: C, 64·0; H, 4·4. $C_{14}H_{11}O_3Cl$ requires C, 63·8; H, 4·2%), and the p'-*bromo-acid*, m.p. 179° (Found: C, 55·1; H, 3·1. $C_{14}H_{11}O_3Br$ requires C, 54·8; H, 3·6%), crystallised from acetic acid in colourless plates.

m-β-*Phenylethoxybenzoic acid*, m. p. 110° (Found: C, 74·2; H, 5·9. $C_{15}H_{14}O_3$ requires C, 74·3; H, 5·8%), and m-γ-*phenyl*-n-*propoxybenzoic acid*, m. p. 118° (Found: C, 74·9; H, 6·2. $C_{16}H_{16}O_3$ requires C, 75·0; H, 6·3%), crystallised similarly.

2 : 5-*Dichlorophenyl ethers.* 2 : 5-Dichlorophenol, m. p. 58°, was prepared by standard methods by the following sequence of reactions: *p*-dichlorobenzene ⟶ 2 : 5-dichloronitrobenzene ⟶ 2 : 5-dichloroaniline ⟶ 2 : 5-dichlorophenol. Its *benzyl* ether, m. p. 58° (Found: * Cl, 27·8. $C_{13}H_{10}OCl_2$ requires Cl, 28·1%), crystallised from ethyl alcohol in clusters of colourless rhombs, and the p-*fluorobenzyl* ether, m. p. 86° (Found: C, 57·6; H, 3·4. $C_{13}H_9OFCl_2$ requires C, 57·6; H, 3·4%), and the m-*fluorobenzyl* ether, m. p. 79° (Found: C, 57·1; H, 3·4%), crystallised similarly. The p-*bromobenzyl* ether had m. p. 77° (Found: C, 47·3; H, 2·7. $C_{13}H_9OCl_2Br$ requires C, 47·0; H, 2·7%), and the p-*methylbenzyl* ether m. p. 58° (Found: * Cl, 26·4. $C_{14}H_{12}OCl_2$ requires Cl, 26·6%).

3 : 5-*Dichlorophenyl ethers.* The 3 : 5-dichlorophenol, m. p. 65°, was a specimen kindly supplied by Dr. A. W. Chapman and prepared by the following series of reactions: *p*-nitroaniline ⟶ 2 : 6-dichloro-*p*-nitroaniline ⟶ 3 : 5-dichloronitrobenzene ⟶ 3 : 5-dichloroaniline ⟶ 3 : 5-dichlorophenol. Methylation by means of methyl sulphate gave 3 : 5-dichloroanisole, which crystallised from ethyl alcohol in colourless, slender prisms, m. p. 40—41° (Found: C, 47·2; H, 3·3. Calc.: C, 47·5; H, 3·4%).

3 : 5-*Dichlorophenyl* p-*bromobenzyl ether* crystallised from alcohol in colourless plates, m. p. 68° (Found: C, 47·1; H, 2·8. $C_{13}H_9OCl_2Br$ requires C, 47·0; H, 2·7%).

4-*Nitro*-o-*tolyl ethers.* These were prepared from a purchased specimen of *p*-nitro-*o*-cresol, m. p. 116°. The methyl ether, m. p. 74°, the ethyl ether, m. p. 60° (Found: * C, 60·0; H, 6·0. Calc.: C, 59·7; H, 6·1%), and the n-*propyl* ether, m. p. 51° (Found: C, 61·5; H, 6·7. $C_{10}H_{13}O_3N$ requires C, 61·5; H, 7·1%), crystallised from ethyl alcohol in colourless slender prisms. The *benzyl* ether, m. p. 79° (Found: * C, 69·5; H, 5·3. $C_{14}H_{13}O_3N$ requires C, 69·1; H, 5·4%), and the p-*methylbenzyl* ether, m. p. 110° (Found: * C, 70·5; H, 6·2. $C_{15}H_{15}O_3N$ requires C, 70·0; H, 5·9%), crystallised from alcohol in clusters of colourless prisms.

m-Fluorophenol was prepared by the decomposition of the diazonium salt of *m*-fluoroaniline, which was itself prepared from *m*-nitroaniline *via m*-fluoronitrobenzene by Balz and Schiemann's method (*Ber.*, 1927, **60**, 1186; cf. Bennett, Brooks, and Glasstone, J., 1935, 1822). The phenol gave with *o*-nitrobenzyl chloride in the usual way *m*-*fluorophenyl* o-*nitrobenzyl ether*, which crystallised from ethyl alcohol in slender yellow prisms, m. p. 53° (Found: * N, 5·69. $C_{13}H_{10}O_3NF$ requires N, 5·67%). These crystals were very sensitive to sunlight, and soon darkened.

m-*Chlorophenyl benzyl ether* crystallised from alcohol in colourless, slender prisms, m. p. 65° (Found: C, 71·3; H, 5·0. $C_{13}H_{11}OCl$ requires C, 71·4; H, 5·1%). The methyl, ethyl, and benzyl ethers of *m*-nitrophenol had m. p.'s 39°, 36°, and 58° respectively.

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115. *Preparation of* 1 : 3-*Dinitronaphthalene.*

By Herbert H. Hodgson and Stanley Birtwell.

Details are given for the preparation of 1 : 3-dinitronaphthalene from 2 : 4-dinitro-1-naphthylamine by the action of cuprous oxide on the diazo-compound in glacial acetic–sulphuric acid solution.

Failure to diazotise 2 : 4-dinitro-1-naphthylamine with preservation of the nitro-groups (Morgan and Evens, J., 1919, **115**, 1126) prevented the preparation of 1 : 3-dinitronaphthalene from this amine, and it was obtained by Veselý and Dvorák (*Bull. Soc. chim.*, 1923, **33**, 323,328) *via* the oxidation of 1 : 3-dinitrotetralin. The diazotisation method of Hodgson and Walker (J., 1923, **123**, 1620) enabled 2 : 4-dinitronaphthalene-1-diazonium sulphate to be prepared free from 4-nitronaphthalene-1 : 2-diazo-oxide, and its decomposition by ethyl alcohol gave 1 : 3-dinitronaphthalene in yields of *ca.* 50%. 1 : 3-Dinitronaphthalene is a potentially useful intermediate and an improved preparation is now described.

The hydrolysis of 2 : 4-dinitro-*p*-toluenesulphon-1-naphthalide by concentrated sulphuric acid at room temperature gives 2 : 4-dinitro-1-naphthylamine in almost theoretical yield; hydrolysis at 70° (Morgan and Evens, *loc. cit.*) or 80° (Hodgson and Smith, J., 1935, 1854) gives a less pure product. The diazonium salt is much more effectually decomposed by cuprous oxide than by ethyl alcohol; this decomposition, however, must be complete, otherwise, when the reaction mixture is poured into water, some 4-nitronaphthalene-1 : 2-diazo-oxide may be formed (detected by treatment with alcohol; the 4-nitro-2-naphthol thus formed will couple with any unchanged diazo-oxide present). The best ratio of sulphuric acid to glacial acetic acid in the solution of the diazonium salt is *ca.* 1 : 3, the solution then being not too viscous to prevent the cuprous oxide from reacting with reasonable speed. Freshly precipitated or commercial cuprous oxide may be used. Reaction above 25° appears to promote slight reduction of the nitro-groups, since diazotisable amine has been detected in some cases. Cupric copper, if present in the cuprous oxide, causes conversion of some of the 2 : 4-dinitronaphthalene-1-diazonium sulphate into 4-nitronaphthalene-1 : 2-diazo-oxide (Hodgson and Birtwell, this vol., p. 321).

1 : 3-Dinitronaphthalene is obtainable from 2 : 4-dinitro-*p*-toluenesulphon-1-naphthalide without isolation of the intermediate 2 : 4-dinitro-1-naphthylamine.

2 : 4-Dinitronaphthalene-1-diazonium sulphate is practically unaffected by hydrazine or hydroxylamine sulphate.

Experimental.

Improved Preparation of 2 : 4-*Dinitro*-1-*naphthylamine.*—2 : 4-Dinitro-*p*-toluenesulphon-1-naphthalide was prepared (Hodgson and Smith, *loc. cit.*) from *p*-toluenesulphon-1-naphthalide (75 g.), washed with water, and stirred into sulphuric acid (200 c.c., *d* 1·84) at such a rate that the temperature could be maintained below 20° by external cooling. After 45 minutes the solution was slowly poured on ice, and the bright lemon-yellow 2 : 4-dinitro-1-naphthylamine collected, washed with water (10 l.), and dried at 65°. The product had m. p. 238—242° and was therefore almost pure (Hodgson and Smith, *loc. cit.*, give m. p. 242° for the recrystallised compound); yield, theoretical. Alternatively, dried 2 : 4-dinitro-*p*-toluenesulphon-1-naphthalide was added to sulphuric acid (185 c.c. of acid, *d* 1·84, and 15 c.c. of water), the subsequent procedure being as described above.

Preparation of 1 : 3-*Dinitronaphthalene.*—(a) *From* 2 : 4-*dinitro*-1-*naphthylamine.* Finely powdered 2 : 4-dinitro-1-naphthylamine (23·5 g.) was dissolved in well-stirred sulphuric acid (90 c.c., *d* 1·84) below 10°, and the solution treated with one of sodium nitrite (7·5 g.) in sulphuric acid (35 c.c., *d* 1·84), the temperature being maintained at or below 10°. The mixture was stirred gradually into glacial acetic acid (375 c.c.) kept below 20°, stirring being continued for 30 minutes thereafter. Cuprous oxide (25 g.) was then vigorously stirred into the solution, initially at 5°, during 15 minutes, the temperature rising to 25—30°; after further stirring for 15 minutes, the evolution of gas ceased. The thick brownish-white liquid was stirred into a mixture of ice (500 g.) and water (2 l.), and the precipitated 1 : 3-dinitronaphthalene collected, washed, and pressed. The moist cake was dissolved in hot pyridine (200 c.c.) and filtered hot from the insoluble copper oxide, which was washed several times with hot pyridine (75 c.c. in all); the hot filtrates, after addition of water (75 c.c.), deposited 1 : 3-dinitronaphthalene (16 g.), m. p. 146—147°, on cooling; further dilution with water afforded 2 g. more (m. p. 138—140°). Total yield, 18 g. (82%). 1 : 3-Dinitronaphthalene crystallised from aqueous pyridine in pale yellow parallelepipeds having a silvery lustre, m. p. 148° (Veselý and Dvorák, *loc. cit.*, describe brownish needles, m. p. 144—145°) (Found: N, 12·9. Calc.: N, 12·8%).

(b) *From* 2 : 4-*dinitro*-p-*toluenesulphon*-1-*naphthalide.* The naphthalide (38·7 g.) was dissolved below 10° in sulphuric acid (90 c.c., *d* 1·84) and mixed at this temperature with nitrosylsulphuric acid prepared from sodium nitrite (8 g.) and sulphuric acid (35 c.c., *d* 1·84). This solution was stirred dropwise into glacial acetic acid (375 c.c.) below 20°. The mixture, after being stirred for 30 minutes to complete the hydrolysis of the 2 : 4-dinitro-*p*-toluenesulphon-1-naphthalide and subsequent diazotisation, was treated with cuprous oxide (25 g.), added during 15—20 minutes; the temperature, which rose to *ca.* 40°, was allowed to fall slowly, evolution of gas ceasing in *ca.* 1 hour. The solution was then poured into ice and water, and the precipitate collected, washed, dried, and extracted with hot ethylene dichloride (250 c.c.). After partial removal of solvent (200 c.c.) from the extract by distillation, 1 : 3-dinitronaphthalene (14·2 g., m. p. 144—146°) separated; it crystallised from ethylene dichloride (charcoal) in pale yellow needles, m. p. 148°. The mother-liquors (above), on evaporation to dryness, afforded a further 2·9 g., the total yield thus being 17·1 g. (78%).

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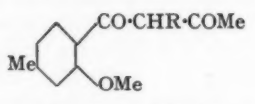
116. *Preparation of 3-Alkylchromones. Effect of Substitution on the Reactivity of the 2-Methyl group in Chromones.*

By Ahmad Zaki and Raymond C. Azzam.

The method of Bloch and Kostanecki has been used in the preparation of a number of 3-alkyl-2-methylchromones.

2-*Methoxy*-4-*methylbenzoylacetone* (I, R = H) and a number of its α-alkyl derivatives (I, R = Me, Et, *n*-Pr, *n*-Bu, *n*-amyl, and CH_2Ph) have been converted into the corresponding *chromones* (II) by boiling hydriodic acid, in yields varying from 83% in the case of (I, R = H) to 66% in the case of (I, R = CH_2Ph) (cf. Bloch and Kostanecki, *Ber.*, 1900, **33**, 471, 1998; Kostanecki and Lloyd, *ibid.*, 1901, **34**, 2942). In all the 2-methylchromones (II) thus produced, the methyl group is reactive and condenses with aromatic aldehydes to give *styryl* derivatives. Thus substitution of alkyl groups in positions 3 and 7 does not affect the usual reactivity of the 2-methyl group (cf. Chakravarti, *J. Indian Chem. Soc.*, 1931, **8**, 25; Heilbron, J., 1934, 1311).

(I.)  (II.)

In the case of the *benzoyl* derivative of (I, R = COPh) the reaction leads to 7-methylflavone, thus showing that the acetyl group is eliminated in preference to the benzoyl group.

Experimental.

2-*Methoxy*-4-*methylbenzoylacetone*.—2-Methoxy-4-methylacetophenone (16·4 g.; 1 mol.) was dissolved in pure ethyl acetate (26·5 g.; 3 mols.), sodium (2·3 g.; 1 mol.) added, and the mixture cooled in ice with occasional shaking. The thick brown broth was left in the ice-box overnight, ice then added, the sodium salt dissolved in cold water, and the solution acidified with the required amount of acetic acid. The oil which separated was extracted in ether and shaken with cold 5% sodium hydroxide solution. The alkaline extract on treatment with carbon dioxide gave a crystalline mass, which was washed with water and recrystallised from alcohol, forming yellowish plates of 2-*methoxy*-4-*methylbenzoylacetone*, m. p. 52° (Found: C, 69·8; H, 7·0. $C_{12}H_{14}O_3$ requires C, 69·9; H, 6·85%).

2 : 7-*Dimethylchromone* (cf. Wittig, *Annalen*, 1926, **446**, 155).—2-Methoxy-4-methylbenzoylacetone (10·6 g.) was boiled with hydriodic acid (40 c.c., *d* 1·96) for 3 hours, and the mixture then poured on ice (100 g.). The oil that separated and soon solidified was dissolved in ether, and the solution washed successively with sodium bisulphite, 5% sodium carbonate and 2% sodium hydroxide solutions. After drying over sodium sulphate, the ether was distilled, and the chromone crystallised from light petroleum (b. p. 80—90°), forming colourless needles, m. p. 98°. Yield, 7·2 g. (83%) (Found: C, 75·6; H, 5·7. Calc. for $C_{11}H_{10}O_2$: C, 75·85; H, 5·8%).

4′-*Methoxy*-2-*styryl*-7-*methylchromone*.—A solution of 2 : 7-dimethylchromone (1·74 g.; 1 mol.) and anisaldehyde (1·36 g.; 1 mol.) in absolute alcohol (10 c.c.) was cooled in ice, sodium ethoxide solution (0·23 g. of sodium in 20 c.c. of absolute alcohol) added, and the mixture left in the ice-box for 24 hours. The brownish-yellow mass was collected, washed with water containing a few drops of acetic acid, and crystallised from light petroleum (b. p. 80—90°), giving small yellow plates of 4′-*methoxy*-2-*styryl*-7-*methylchromone*, m. p. 150° (Found: C, 77·8; H, 5·5. $C_{19}H_{16}O_3$ requires C, 78·05; H, 5·5%).

α-2-*Methoxy*-4-*methylbenzoyl*-α-*methylacetone*.—2-Methoxy-4-methylbenzoylacetone (20·6 g.) was dissolved in absolute alcohol (60 c.c.), and sodium ethoxide solution (2·3 g. of sodium in 40 c.c. of absolute alcohol) added, followed after 10 minutes by methyl iodide (20 g.); the mixture was refluxed until it was neutral to litmus (about 20 mins.). The solution was filtered, alcohol and the excess of methyl iodide distilled off, and the residual oil distilled under diminished pressure. α-2-*Methoxy*-4-*methylbenzoyl*-α-*methylacetone* was obtained as a thick yellow oil, b. p. 190—192°/20 mm. (Found: C, 70·7; H, 7·2. $C_{12}H_{16}O_3$ requires C, 70·9; H, 7·3%).

2 : 3 : 7-*Trimethylchromone*.—This chromone (Robertson, Waters, and Jones, J., 1932, 1681) was prepared in the general way described above, from α-2-methoxy-4-methylbenzoyl-α-methylacetone (11 g.). Yield, 7·3 g. (78%). Recrystallised from petrol, it formed colourless needles, m. p. 89° (Found: C, 76·5; H, 6.4. Calc.: C, 76·6; H, 6·4%).

4′-*Methoxy*-2-*styryl*-3 : 7-*dimethylchromone*, prepared from 2 : 3 : 7-trimethylchromone (1·88 g.), crystallised from alcohol in long, yellow, silky needles, m. p. 123° (Found: C, 78·2; H, 6·0. $C_{20}H_{18}O_3$ requires C, 78·4; H, 5·9%).

α-2-*Methoxy*-4-*methylbenzoyl*-α-*ethylacetone* was obtained as a thick yellow oil, b. p. 197—200°/20 mm. (Found: C, 71·3; H, 7·8. $C_{14}H_{18}O_3$ requires C, 71·75; H, 7·75%).

2 : 7-*Dimethyl*-3-*ethylchromone*, obtained as a liquid by Robertson, Waters, and Jones (*loc. cit.*), was prepared by the general method described above from α-2-methoxy-4-methylbenzoyl-α-ethylacetone (11·7 g.). After removal of the ether a reddish oil was obtained (7·8 g.), which was distilled; the portion, b. p. 300—305°, solidified on cooling and crystallised from light petroleum (b. p. 30—50°) in small colourless needles, m. p. 51°; yield, 78% (Found: C, 77·0; H, 7·15. Calc.: C, 77·2; H, 7·0%).

4′-*Methoxy*-2-*styryl*-7-*methyl*-3-*ethylchromone*, prepared from 2 : 7-dimethyl-3-ethylchromone (2 g.), separated from acetic acid in yellow crystals, m. p. 114° (Found: C, 78·6; H, 6·25. $C_{21}H_{20}O_3$ requires C, 78·7; H, 6·3%).

α-2-*Methoxy*-4-*methylbenzoyl*-α-n-*propylacetone*.—This and the following alkyl diketones could not be obtained by the method used for the methyl analogue. The sodium salt precipitated from the alcoholic solution of the diketone by the addition of sodium ethoxide solution was therefore collected, washed with absolute alcohol, dried in a desiccator, and suspended in a large excess of *n*-propyl iodide and the mixture was refluxed until it was neutral to litmus. After filtration and distillation of the excess of propyl iodide the residual oil was fractionated under diminished pressure; the fraction, b. p. 206—210°/20 mm., consisted mainly of α-2-*methoxy*-4-*methylbenzoyl*-α-n-*propylacetone* (Found: C, 72·2; H, 8·0. $C_{15}H_{20}O_3$ requires C, 72·5; H, 8·1%).

2 : 7-*Dimethyl*-3-n-*propylchromone* was prepared from α-2-methoxy-4-methylbenzoyl-α-*n*-propylacetone (12·4 g.). The viscous oil (7·6 g.) obtained crystallised from light petroleum in colourless needles, m. p. 56—57°. Yield, 71% (Found: C, 77·5; H, 7·35. $C_{14}H_{16}O_2$ requires C, 77·7; H, 7·5%).

4′-*Nitro*-2-*styryl*-7-*methyl*-3-n-*propylchromone*, prepared from 2 : 7-dimethyl-3-*n*-propylchromone (2·2 g.) and 4-nitrobenzaldehyde (1·5 g.), crystallised from acetic acid in small yellow plates, m. p. 176—177° (Found: C, 71·8; H, 5·4; N, 4·0. $C_{21}H_{19}O_4N$ requires C, 72·2; H, 5·5; N, 4·0%).

α-2-Methoxy-4-methylbenzoyl-α-n-butylacetone, a thick yellow oil, b. p. 207—210°/10 mm. (Found: C, 73·1; H, 8·6. $C_{16}H_{22}O_3$ requires C, 73·2; H, 8·4%), was converted into 2 : 7-dimethyl-3-*n*-butylchromone, a viscous reddish oil (yield, 73%), which was identified as its styryl derivative, *4′-nitro-2-styryl-7-methyl-3-n-butylchromone*; this crystallised from acetic acid in long, yellow, silky needles, m. p. 168—170° (Found: C, 72·45; H, 5·75; N, 3·9. $C_{28}H_{21}O_4N$ requires C, 72·7; H, 5·8; N, 3·8%).

α-2-Methoxy-4-methylbenzoyl-α-n-amylacetone, a yellow thick oil, b. p. 215—220°/10 mm. (Found: C, 73·9; H, 8·9. $C_{17}H_{24}O_3$ requires C, 73·9; H, 8·8%), was converted into 2 : 7-dimethyl-3-*n*-amylchromone (yield, 72%), a viscous reddish oil identified in the form of *4′-nitro-2-styryl-7-methyl-3-n-amylchromone*, which crystallised from benzene–light petroleum in yellow needles, m. p. 173—174° (Found: C, 73·7; H, 6·12; N, 3·8. $C_{29}H_{29}O_4N$ requires C, 73·2; H, 6·15; N, 3·7%).

α-2-Methoxy-4-methylbenzoyl-α-benzylacetone.—The dry sodium salt of the diketone was suspended in dry benzene and refluxed with benzyl bromide until the mixture was neutral to litmus. After removal of sodium bromide by filtration and of benzene by distillation the residual oil solidified on cooling. It crystallised from light petroleum (b. p. 50—60°) in long colourless needles, m. p. 67—68° (Found: C, 77·3; H, 7·0. $C_{19}H_{20}O_3$ requires C, 77·0; H, 6·8%).

3-Benzyl-2 : 7-dimethylchromone, prepared from α-2-methoxy-4-methylbenzoyl-α-benzylacetone (14·8 g.), crystallised from benzene–light petroleum in colourless needles, m. p. 95°. Yield, 66% (Found: C, 81·8; H, 6·0. $C_{18}H_{16}O_2$ requires C, 81·8; H, 6·1%).

4′-Methoxy-2-styryl-3-benzyl-7-methylchromone crystallised from alcohol in yellow needles, m. p. 176° (Found: C, 81·4; H, 5·9. $C_{26}H_{22}O_3$ requires C, 81·6; H, 5·8%).

α-Benzoyl-α-2-methoxy-4-methylbenzoylacetone.—To a solution of 20·6 g. of 2-methoxy-4-methylbenzoylacetone in 75 c.c. of absolute alcohol, cooled in ice, 50 c.c. of sodium ethoxide solution (4·6 g. of sodium) and 12 c.c. of benzoyl chloride were alternately added in ten successive portions, the flask being removed from the ice for 5 minutes after each addition. After 12 hours ice-cold water was added, and the solution acidified with acetic acid. The thick oil which separated was taken up in ether and shaken with cold 5% sodium hydroxide solution, the benzoyl derivative, being more acidic than the original diketone, dissolving first in the alkali. The alkaline solution was acidified with acetic acid and the oil formed was taken up in ether. The ethereal solution was left overnight with anhydrous sodium sulphate. A portion of the compound crystallised; it was filtered off together with the sodium sulphate, from which it was separated by water. After crystallisation from light petroleum colourless crystals were obtained, m. p. 141—148°. From the ethereal solution a mixture of a solid and an oil was obtained. The solid, crystallised from light petroleum, had m. p. 137—139°. Neither solid gave a colour with ferric chloride, but the liquid gave a violet colour. It seems that the liquid is the enolic form and the two solids are enantiomorphic keto-forms of *α-benzoyl-α-2-methoxy-4-methylbenzoylacetone*. On standing, and after repeated crystallisation, the two solids gave a substance, m. p. 134—151° (Found: C, 77·4; H, 6·1. $C_{18}H_{18}O_4$ requires C, 77·5; H, 6·2%). When boiled with hydriodic acid, this substance gave a compound, m. p. 122—123°, which did not condense with aromatic aldehydes and was identified as 7-methylflavone.

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117. *The Structure of Molecular Compounds. Part II.*

By H. M. POWELL and G. HUSE.

Evidence from melting points, and the intensities of reflexion of *X*-rays, including diffuse spectra, of crystals of intermolecular compounds is against the existence of ions in the structures. The structures of the intermolecular compounds of the picryl halides and hexamethylbenzene are very complex and disordered to some extent. They consist of alternate layers of the two components, and the binding between the layers, and therefore between the two kinds of molecule, is shown to be weak.

IN Part I (this vol., p. 153) it is shown that molecular-compound formation between *s*-trinitrobenzene and *p*-iodobenzene is not due to the production of any covalent bond between the molecules. There may be very weak hydrogen bonds between amino-groups and oxygen atoms of nitro-groups, but these do not seem to be an essential feature of the compound formation. It has been suggested (Weiss, J., 1942, 245) that all the properties of these molecular compounds may be explained by assuming the formation of a complex molecule, ionic in character, through transfer of an electron from a hydrocarbon, or its derivative, to the polynitro-compound. It is apparently envisaged that in the crystal structures of these compounds the carbon atoms of the component ions will be about 3·2 A. from each other. This is not the case for the compound studied, and the interatomic distances observed are about normal for intermolecular distances in typical organic crystals. In this paper some evidence bearing on the ionic hypothesis is considered.

Whether or not the component parts in a crystal of a molecular compound are held together by ionic bonds may be considered independently of interatomic distances by a study of the strengths of the crystals. In general, a crystal in which electrostatic attraction between oppositely charged ions is one of the binding forces, will have greater strength than one containing geometrically comparable molecules held by weaker forces, *e.g.*, forces of van der Waals type. This reveals itself in the greater hardness and higher melting point of the ionic crystal. Since the thermal movements of the atoms are of greater amplitude in the weaker crystal, it also shows in the falling off in intensity of all *X*-ray reflexions as the Bragg angle θ increases, which is more marked in the weaker crystal. A further way in which the strength of the crystal may be revealed is in the production of "diffuse" *X*-ray reflexions. The origin of diffuse reflexions is disputed and such reflexions have been observed from crystals in which all kinds of interatomic binding are operative; but it is only in crystals where there are planes held by weak forces that the diffuse spectra are of such intensity that they may be observed with the relatively short exposures in an ordinary moving-crystal oscillation or Weissenberg photograph. The effect is readily interpreted on the elastic vibration theory as due to the large atomic movements perpendicular to a plane, as, *e.g.*, the basal plane in graphite, favoured by weak inter-layer binding. In this case the diffuse spectra may appear as backgrounds to the normal Bragg reflexions of the corresponding planes. In basing any

conclusions on the existence of such reflexions it is clearly necessary to consider the whole structure, since the interatomic forces, in a different direction may, as in graphite, be of a different kind.

The following table gives the melting-point data for a number of molecular compounds, together with the m. p.'s of the components. The m. p. of the compound is usually lower than that of one of the components, and if the two components have nearly the same m. p. the compound may melt at a lower temperature than either of them. This indicates that the intermolecular binding forces in the compound are not markedly greater than those in the molecular crystals of the component substances.

Melting points of A, B, *and their molecular compound* AB.

		Melting points.		
A.	B.	A.	B.	AB.
Aniline	*s*-Trinitrobenzene	−8°	122°	123°
2 : 4 : 6-Tribromoaniline	,,	118·5	122	108·5
p-Chloroaniline	,,	71	122	110
p-Iodoaniline	,,	63	122	108
3 : 5-Di-iodo-*p*-toluidine	,,	125·5	122	95·5
Hexamethylbenzene	Picryl chloride	164	83	148
,,	,, bromide	164	122	151
,,	,, iodide	164	165	145

X-Ray photographs do not show any evidence of increased hardness that would be expected for an ionic crystal. In Fig. 1 it may be seen that for picryl iodide, which is unusually hard for an organic crystal, the falling off in *X*-ray intensities as the Bragg angle θ increases is not so marked as for the molecular compound of *p*-iodoaniline and trinitrobenzene.

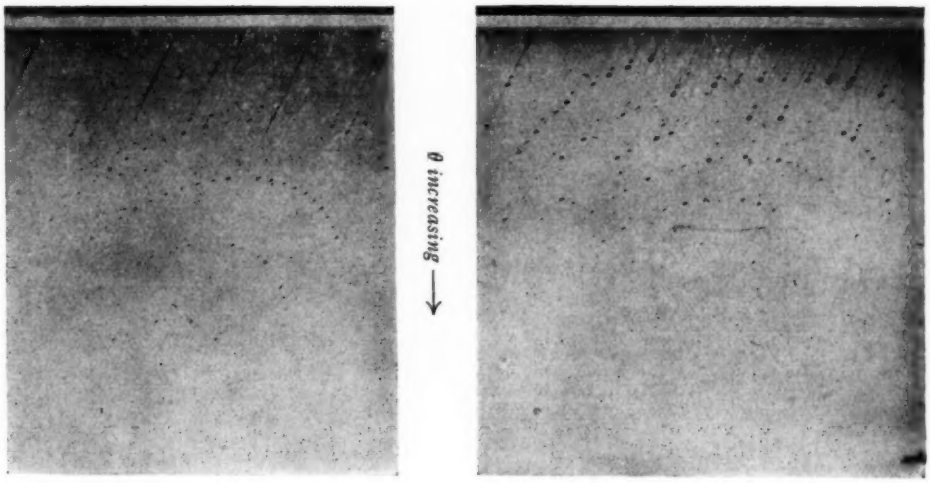
Diffuse *X*-ray reflexions have been observed from crystals of several molecular compounds. They were not observed for the *p*-iodoaniline–*s*-trinitrobenzene compound for which the structure is most completely known, and it should be noted that in this structure the planes of the molecules are not all parallel to any one plane of the crystal. When the molecular planes are all parallel, diffuse reflexions are observed, the most significant case being that of the compounds of hexamethylbenzene with picryl halides. These compounds have a structure which is to some extent disordered; the unit cell contains 336 (or possibly 1344) atoms, exclusive of hydrogen, and this complexity, added to the disorder, makes it difficult to determine the complete structure, but the essential part is known with certainty.

The compound of picryl chloride and hexamethylbenzene forms bright yellow, orthorhombic crystals, pseudo-hexagonal prisms showing the main forms {100}, {001}, {011}; m. p. 148°; d 1·37$_5$ g./c.c. They show strong negative double refraction, with acute bisectrix along [100] and optic axial plane parallel to (001), and there is marked dispersion ($v > \rho$) of the optic axial angle. *X*-Ray oscillation and Weissenberg photographs show an apparent unit cell with $a = 14{\cdot}0$, $b = 9{\cdot}0$, $c = 15{\cdot}4$ A., having four molecules of each component per cell. From the absent spectra, the space group is A*ma* or A*mam*. In addition to the diffraction pattern due to this cell there are streaks which indicate irregularity in the a spacing, and suggest that the true b dimension should be three times that given above. The picryl bromide compound is very similar in morphology, optical properties, and the intensities of corresponding *X*-ray reflexions. The dimensions of the pseudo-cell are $a = 14{\cdot}0$, $b = 9{\cdot}13$, $c = 15{\cdot}32$ A. Additional streaks similar to those given by the chloride are observed, but they are much more intense, and for certain positions they group into smudged-out spots on intermediate layer or row lines corresponding to the unit cell with trebled b spacing. The picryl iodide compound is similar in form and optical properties to the other two. The a and c dimensions are about the same as those of the bromide, and b has a definite value, approximately three times that of the pseudo-cells of the chloride and bromide. The irregular streaks and smudges have, in this compound, become sharp spots on intermediate layer lines, but there is still some irregularity shown by a tendency to continuous row lines in rotation photographs about the A axis. These lines tend to split into spots on layers corresponding to a fourfold enlarged a spacing. If this is disregarded, the cell dimensions are $a = 14{\cdot}15$, $b = 27{\cdot}98$, $c = 15{\cdot}16$ A. The density is 1·6 g./c.c., and there are twelve molecules of each component in the unit cell: space group A*ma* or A*mam*.

In addition to the extra reflexions, arising from the disorder in the lattice, diffuse reflexions are observed. These are not so sharp as many of the extra reflexions and there are few of them. There is one particularly intense diffuse reflexion which appears as background to the strong Bragg reflexion 400. It is easily observed in an ordinary oscillation photograph (Fig. 2).

If, in the first place, the apparent unit cell and space group of the chloride is taken as a basis, then the value of the a spacing, optical properties, and the alternation in intensities of $h00$ reflexions all combine to indicate that the structure consists of alternate layers of the two components parallel to (100). This is confirmed by the Patterson–Fourier projection normal to [001], which shows only four ridges of high P(xy) value, spaced out at equal intervals of 3·5 A. along the a direction. The interatomic vectors with a components of zero or 7 A. combine to produce much higher ridges at those distances than at 3·5 and 10·5 A. In the Patterson–Fourier projection for the iodide, all the reflexions corresponding to the treble-size unit cell are used and a similar result is obtained (Fig. 3). The only interpretation possible is that there are four layers of molecules parallel to (100) equally spaced at 3·5 A. and that each layer consists of one kind of molecule only. This conclusion is confirmed completely by calculation of the intensities of reflexion $h00$. For these calculations the picryl

FIG. 1.

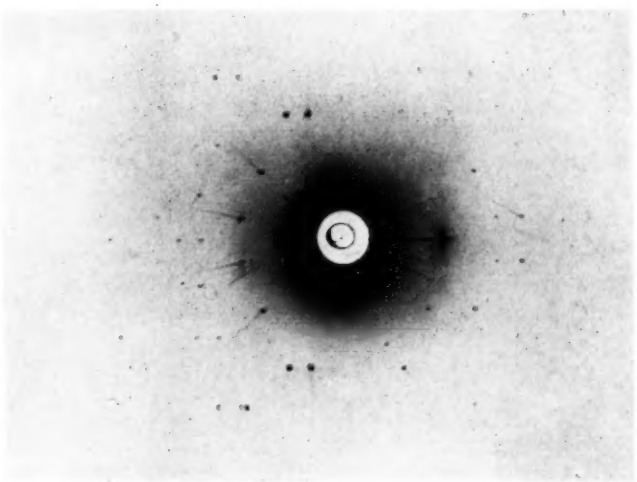


Part of Weissenberg photograph of picryl iodide. Reflexions extending to high values of θ.

Part of Weissenberg photograph of the compound of p*-iodoaniline and* s*-trinitrobenzene. Reflexions fade off more rapidly with increasing θ.*

FIG. 2.

Oscillation photograph of picryl chloride–hexamethylbenzene, showing diffuse reflexions 400 (*strong*) *and* 402 (*faint*).



[*To face p.* 436.

halide molecules are assumed planar except for the oxygen atoms of the two nitro-groups in the *o*-positions to the halogen, which are taken to be turned up out of the plane as in picryl iodide (Huse and Powell, J., 1940, 1398). The agreement shown in the following table is destroyed if mixed layers are assumed. The structure is thus established as far as the relative disposition of the molecules along the *a* axis is concerned. It is easy

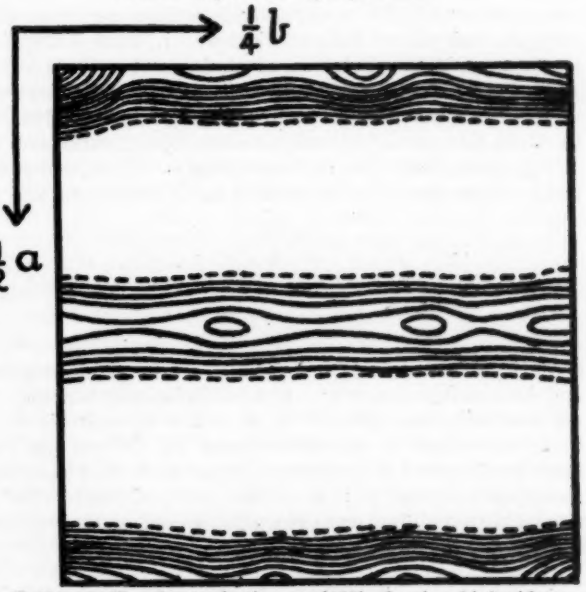
Calculated and observed values of F(*h*00). (Temperature correction with $B = 4$ applied.)

	$h =$	2.	4.	6.	8.	10.	12.
Picryl chloride–hexamethylbenzene	F relative, obs.	30	91	13	43	6	16
	F/12, calc.	32	94	4	34	1	16
Picryl iodide–hexamethylbenzene	F relative, obs.	58	140	48	80	23	30
	F/12, calc.	69	124	24	58	19	38

to arrange the hexamethylbenzene molecules in the available space so that the layer is almost identical with a single layer of the structure in hexamethylbenzene itself, and it seems probable that they have this arrangement. Very extensive trials made to determine the distribution of the picryl halide molecules in their layers will not be considered here since the problem has not been completely solved. A possible explanation of the complexities of the structure is that the sequence of layers is not a completely regular one, and that, owing to the great similarity of the structure of the hexamethylbenzene layer to that of the pure hydrocarbon, there are occasional regions where an extra layer of hexamethylbenzene is added, the crystal growing momentarily as though it were one of hexamethylbenzene only. This could result in the almost continuous distribution of *a* spacing represented by the observed streaks. Owing to the pseudo-hexagonal character of the hydrocarbon layers, there are three ways of placing a picryl halide molecule relative to the hexamethylbenzene molecules which are geometrically almost equivalent. One way of accounting for the trebling of the *b* dimension is to suppose that all three ways are used. A regular sequence of the molecules in the three alternative positions would give the true larger unit cell of the iodide, a less regular arrangement with a preponderance of molecules in regular array would produce the smudged-out spots on intermediate layer lines as in the bromide, and the pseudo-cell observed for the chloride would be due to the almost completely random distribution of molecules in the three positions.

FIG. 3.

Hexamethylbenzene–picryl iodide.



Patterson–Fourier projection on (001) *showing high ridges separated by* ½a (7 A.), *and lower ridge half way between.*

The intense diffuse reflexion observed as background to 400 is readily explained in terms of the structure, since it is from the plane of the flat molecules. Another faint diffuse reflexion 402 is from a plane slightly inclined to the plane of the molecules. These reflexions are similar to those given by other molecular crystals containing flat parallel molecules, and show that there is weak binding between the layers. Since all molecules in a given layer are of one kind, and each layer is related in the same way to both its neighbouring layers, there must be weak binding between the two kinds of molecule; the conclusion is independent of the detailed structure in the layers. All the evidence on the strength of these crystals is thus against the existence of ions in the structure; what interaction there is between the component molecules does not appear to be greater than the mutual interaction of molecules of a nitro-compound such as picryl iodide, in its crystals, where the transfer of an electron with formation of oppositely charged ions would not be postulated.

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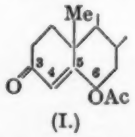
118. *Acyl Migrations in the Sterol Series.*

By M. F. C. PAIGE.

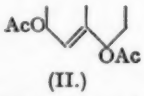
In connection with a project for the conversion of cholesterol into hyodeoxycholic acid and its stereoisomerides a study has been made of possible new methods of preparation of 6(β)-acetoxy-Δ⁴-cholesten-3-one (I). In the course of this work an investigation was made of the acyl migrations which take place with 3-monoesters (VII) of *cis*-Δ⁵-cholestene-3 : 4-diol. Evidence is adduced that this migration proceeds through the intermediate formation of an orthocarbonate (VIII).

HYODEOXYCHOLIC acid (3 : 6-dihydroxycholanic aid) has been isolated from pigs' bile, and its structure determined (Windaus and Bohne, *Annalen*, 1923, **433**, 278; Windaus, *ibid.*, 1926, **447**, 233; Wieland and Gumlich, *Z. physiol. Chem.*, 1933, **215**, 18). The isolation from the same source of an epimeric 3 : 6-dihydroxycholanic acid was claimed by Kimura (*ibid.*, 1937, **248**, 280). The preparation of hyodeoxycholic acid from a sterol has not yet been recorded, although this bile acid has been degraded stepwise to androsterone (Dalmer *et al.*, *Ber.*, 1935, **68**, 1814). The experiments now described were initiated as part of a project to obtain 3 : 6-dihydroxycholanic acids from cholesterol and to study the configurational relationships between hyodeoxycholic acid and its epimerides, three of which are theoretically possible. In a preliminary investigation of possible routes from cholesterol the issue became somewhat confused by the occurrence of acyl migrations of the type described by Spring and Swain (*Nature*, 1940, **146**, 718; J., 1941, 83) and by Rosenheim (*Nature*, 1941, **147**, 776; Petrow, Rosenheim, and Starling, this vol., p. 135), and it is with these migrations that the present communication is mainly concerned. When the author's experiments were complete Dr. Rosenheim kindly placed at his disposal the typescript of the detailed paper of Petrow, Rosenheim, and Starling, and it is satisfactory that the two lines of approach have led to the same general conclusions as to the mechanism of the migrations.

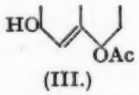
6(β)-Acetoxy-Δ⁴-cholesten-3-one (I) seemed a suitable intermediate for use in the conversion of cholesterol into the desired bile acids, and attempts were made to obtain this unsaturated ketone by a more convenient method than that of Ellis and Petrow (J., 1939, 1078). As 3(β) : 6(β)-diacetoxy-Δ⁴-cholestene (II) is obtainable in 25% yield by oxidation of cholesteryl acetate with selenium dioxide (Butenandt and Hausmann, *Ber.*, 1937, **70**, 1154), its partial hydrolysis to 6(β)-acetoxy-Δ⁴-cholesten-3(β)-ol (III) would probably afford such a method (compare Marker and Krueger, *J. Amer. Chem. Soc.*, 1940, **62**, 79; Ellis and Petrow, *loc. cit.*). Attempts to effect this partial hydrolysis were unsuccessful, and attention was therefore directed to the production of a mixed ester of the diol corresponding to (II) in which the ester group at position 3 would be more susceptible to hydrolysis than that at position 6. For this purpose a study was made of the oxidation of 3-*O*-carbomethoxy-



(I.)

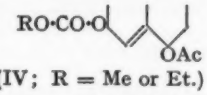


(II.)

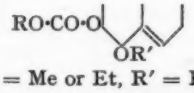


(III.)

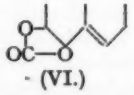
cholesterol with selenium dioxide in acetic acid and acetic anhydride solution. From the results of Butenandt and Hausmann (*loc. cit.*; cf. Rosenheim and Starling, J., 1937, 377) it was anticipated that this would give the desired mixed ester (IV; R = Me) in addition to the 3-*O*-carbomethoxy-derivative of *cis*-Δ⁵-cholestene-3 : 4-diol and/or its 4-acetate (type V). When the oxidation was carried out in acetic anhydride solution there was formed a mixture of products from which the only pure compound isolated was 3-O-*carbomethoxy*-4-*acetoxycholesterol* (V; R = Me; R′ = COMe). The 3 : 6-ester (the product of an allylic rearrangement) was not isolated, but was evidently formed, as hydrolysis of the uncrystallisable residues yielded a small amount of Δ⁴-cholestene-3 : 6-diol.



(IV; R = Me or Et.)



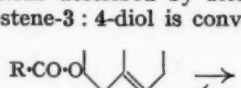
(V; R = Me or Et, R′ = H or COMe.)



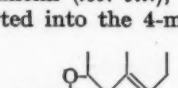
(VI.)

When 3-*O*-carbomethoxycholesterol was oxidised with selenium dioxide in acetic acid solution, the 4-acetoxy-derivative (V; R = Me, R′ = COMe), m. p. 161°, was again isolated, together with a second crystalline product, m. p. 173°. As in the former experiment, the formation of the desired 3 : 6-ester was shown only by the isolation of the 3 : 6-diol after hydrolysis. The compound, m. p. 173°, like 3-*O*-carbomethoxy-4-acetoxycholesterol, gave *cis*-Δ⁵-cholestene-3 : 4-diol on hydrolysis, but was evidently not the 4-hydroxy-derivative of 3-*O*-carbomethoxycholesterol, as it could not be acetylated or benzoylated. This compound was shown, by its independent preparation from *cis*-Δ⁵-cholestene-3 : 4-diol and carbonyl chloride, to be the *carbonate* (VI) of the 3 : 4-diol. The selenium dioxide oxidation of 3-*O*-carbethoxycholesterol in acetic anhydride solution gave 3-O-*carbethoxy*-4-*acetoxycholesterol* (V; R = Et; R′ = COMe) together with a compound of the type sought, namely, 3-O-*carbethoxy*-6-*acetoxy*-Δ⁴-*cholesten*-3-*ol* (IV; R = Et). The structure of the latter compound was shown by its hydrolysis to Δ⁴-cholestene-3 : 6-diol. When the oxidation was carried out in acetic acid solution, the same two products were isolated, together with the carbonate (VI).

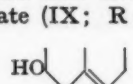
The formation of the carbonate (VI) of the 3 : 4-diol is of interest in connection with the mechanism of the acyl migrations described by Rosenheim (*loc. cit.*), who found that the 3-monoacetate (VII; R = Me) of *cis*-Δ⁵-cholestene-3 : 4-diol is converted into the 4-monoacetate (IX; R = Me) by warming its solution in



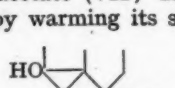
(VII.)



(VIII.)



(IX.)



(X.)

acetic acid to 90°. Rosenheim regarded this as proceeding through the intermediate cyclic acetal (VIII; R = Me), but also drew attention to an alternative mechanism involving the intermediate formation of a

labile pentacyclic compound (X; R = Me) related to *i*-cholesterol. It would appear that the first product of oxidation of 3-*O*-carbomethoxycholesterol in acetic acid solution is its 4-hydroxy-derivative (V; R = Me, R′ = H), which then rearranges to the orthocarbonate (VIII; R = OMe). In this case, however, the intermediate (VIII) becomes stabilised by loss of methyl alcohol to give the carbonate (VI), rather than by further rearrangement to the 4-monoester (IX; R = OMe). In support of this interpretation it was found that the 3-*O*-carbomethoxy- and the 3-*O*-carbethoxy-derivative of *cis*-Δ^5-cholestene-3 : 4-diol were transformed into the carbonate (VI) by boiling acetic or propionic acid.

The isolation of the carbonate in these rearrangements of the 3-*O*-carbomethoxy- and -carbethoxy-compounds affords strong evidence that the mechanism of the acyl migration in 3-monoesters of cholestenediol is as formulated above (VII $\rightleftharpoons$ VIII $\rightleftharpoons$ IX). Additional evidence was furnished by the rearrangement of the 3-monoacetate by hot propionic acid; this gave the 4-monoacetate, and not the propionate which would be anticipated from an intermolecular mechanism involving intermediate formation of (X). Moreover, the rearrangement in propionic acid took place to a smaller extent than in the more strongly acidic acetic acid; even in acetic acid it was incomplete in 6 hours, indicating an equilibrium reaction (compare Petrow, Rosenheim, and Starling *loc. cit.*).

In an attempt to reverse the change and transform the carbonate (VI) into the 3-monoacetate (VII : R = Me) and/or its isomer (IX; R = Me) the carbonate was treated with methylmagnesium iodide (compare Tschitschibabin, *Ber.*, 1905, **38**, 561). The attempt failed on account of the reducing action of the Grignard reagent, which led to Δ^4-cholestene as the only isolable product.

The mixed esters of *cis*-Δ^5-cholestene-3 : 4-diol formed by the action of selenium dioxide on 3-*O*-carbomethoxy- or -carbethoxy-cholesterol in acetic anhydride were hydrolysed to the 3 : 4-diol, and their structures were confirmed by the preparation of the same esters by carbomethoxylation or carbethoxylation of the diol, followed by acetylation of the mono-esters. It is known that monoacylations of this diol take place on the hydroxyl group at C_3 (Rosenheim and Starling, *loc. cit.*; Petrow and Starling, J., 1940, 63; Rosenheim, *loc. cit.*; compare Spring and Swain, J., 1941, 83). The same esters (V; R = Me or Et, R′ = COMe) were also formed by treatment of the 4-monoacetate (IX; R = Me) in pyridine solution with methyl and ethyl chloroformate.

Marker and Rohrmann (*J. Amer. Chem. Soc.*, 1939, **61**, 3022) oxidised cholesteryl acetate in benzene–acetic acid solution with selenium dioxide and isolated two compounds which they regarded as polymorphic forms of 4-hydroxycholesteryl acetate. Reinvestigation of this reaction showed that one of Marker's products is 4-acetoxycholesterol, so the two compounds are structural isomerides. A similar conclusion regarding these "polymorphs" was independently reached by Petrow, Rosenheim, and Starling (*loc. cit.*).

In connection with the original objective of the investigation the catalytic hydrogenation of 6(β)-acetoxy-Δ^4-cholesten-3-one (I) was examined, with palladium, followed by platinum. It was hoped in this way to obtain 6-acetoxy*epi*coprostanol. However, although hydrogen was rapidly absorbed, a crystalline product could not be isolated. Reduction of the acetoxy-ketone (I) with sodium and amyl alcohol gave a resinous product, from which was isolated, after benzoylation, the dibenzoate of cholestane-3(β) : 6(α)-diol. This diol was also formed by similar reduction of cholesterol α- and β-oxides. Hydrogenation of the benzoate of cholesterol β-oxide could not be effected with Adams's platinum oxide catalyst. The slow catalytic hydrogenation of cholesterol α-oxide with palladium in acetic acid was described by Stavely (*J. Amer. Chem. Soc.*, 1942, **64**, 2723). Reduction of Δ^4-cholestene-3 : 6-diol with sodium and amyl alcohol gave a hydrocarbon, m. p. 79—80°, which on catalytic hydrogenation took up one molecule of hydrogen to give cholestane. This product was not Δ^5-cholestene. Its m. p. corresponds with that given in the literature for Δ^4-cholestene, the formation of which involves reduction of both hydroxyl groups of the diol.

Experimental.

A. *Selenium Dioxide Oxidations.*—*3-O-Carbomethoxycholesterol in acetic anhydride solution.* A solution of 3-*O*-carbomethoxycholesterol (4·6 g.) (Robberecht, *Bull. Soc. chim.*, 1938, **47**, 597) in acetic anhydride (100 c.c.) was treated dropwise at 105—110° with a solution of selenium dioxide (2·5 g.) in water (5 c.c.). The temperature was maintained at 105—110° for 2 hours, and the cooled solution decomposed with cold water. The product was extracted with acetone, and the extract slowly added to well-stirred 10% aqueous potassium cyanide, stirring being continued for 4 hours. This served to complete the removal of selenium. The oxidation products were extracted with ether, and the dried extract freed from solvent. Trituration of the residual brown gum with cold alcohol gave crystals which, after two recrystallisations from alcohol, formed a colourless, microcrystalline powder, m. p. 160·5—161° (Found: C, 74·1; H, 9·6. $C_{31}H_{50}O_5$ requires C, 74·1; H, 10·0%). This compound, 3-*O*-*carbomethoxy*-4-*acetoxycholesterol* (V; R = Me, R′ = COMe), was unaffected by 1 hour's boiling with acetic anhydride and was hydrolysed by boiling 5% methyl-alcoholic potash to *cis*-Δ^5-cholestene-3 : 4-diol, m. p. 174° alone or mixed with an authentic specimen.

This mixed ester was also obtained by two other methods. (*a*) Pure pyridine (5 c.c.) was added dropwise, with shaking, to an ice-cooled solution of 4-hydroxycholesterol (1 g.) in anhydrous ether (20 c.c.), benzene (20 c.c.), and methyl chloroformate (5 c.c.). After 2 hours at room temperature the solution was filtered from pyridine hydrochloride, and solvents removed under reduced pressure. Water was added to the residue, and the resulting solid crystallised several times from alcohol, giving thin colourless plates of 3-O-*carbomethoxy*-4-*hydroxycholesterol*, m. p. 157·5—159·5° (Found: C, 75·5; H, 10·7. $C_{29}H_{48}O_4$ requires C, 75·65; H, 10·4%). This (200 mg.) was acetylated by boiling for 1 hour with acetic anhydride (5 c.c.); the cooled solution was poured into ice-water, kept overnight, and the product crystallised from alcohol. The resulting microcrystalline powder had m. p. 160·5—161°, not depressed by the 4-acetoxy-derivative formed by oxidation of 3-*O*-carbomethoxycholesterol. Benzoylation of 3-*O*-carbomethoxy-4-hydroxycholesterol, with benzoyl chloride in pyridine at 100°, gave 3-O-*carbomethoxy*-4-*benzoyloxycholesterol*, rectangular platelets (from acetone–alcohol), m. p. 173—174° (Found: C, 76·5; H, 9·2. $C_{36}H_{52}O_5$ requires C, 76·6; H, 9·2%).

(*b*) The 4-monoacetate of *cis*-Δ^5-cholestene-3 : 4-diol (prepared by rearrangement of the 3-monoacetate in acetic

acid at 90°) (0·33 g.) was treated in the manner described above with methyl chloroformate (3·5 c.c.) and pyridine (6 c.c.). The same mixed ester, m. p. 160·5—161°, was obtained.

The gum formed in the above selenium dioxide oxidation, after removal of the mixed ester, m. p. 161°, was hydrolysed with boiling methyl-alcoholic potash. The resulting crystals, recrystallised from acetone–chloroform, formed colourless fine needles, m. p. 256—257°, and were shown by mixed m. p. to consist of Δ^4-cholestene-3 : 6-diol.

Oxidation of 3-O-*carbomethoxycholesterol in acetic acid solution.* 3-*O*-Carbomethoxycholesterol (21 g.) was dissolved in acetic acid (200 c.c.) at 100°, and mixed with a solution prepared by addition of acetic acid (200 c.c.), heated to 100°, to a solution of selenium dioxide (10 g.) in water (5 c.c.). After 5 minutes' boiling, sodium acetate (60 g.) was added, and boiling continued for a further 5 minutes. The hot solution was filtered from selenium, cooled, poured into half-saturated brine (1000 c.c.), and extracted with ether. The extracts were washed with sodium carbonate solution and with water and dried (sodium sulphate), and the ether removed. Trituration of the residue with cold methyl alcohol gave a crystalline material (2·7 g., m. p. 126—139°), from which two pure products were separated by fractional crystallisation from alcohol. The less soluble product was shown to be 3-*O*-carbomethoxy-4-acetoxycholesterol, m. p. 161°; the more soluble product crystallised from alcohol in colourless leaflets, m. p. 173—173·5°, and was the *carbonate* (VI) of *cis*-Δ^5-cholestene-3 : 4-diol (Found: C, 78·7, 78·4; H, 11·1, 10·7. $C_{29}H_{44}O_3$ requires C, 78·5; H, 10·3%). This compound was unaffected by boiling acetic anhydride or by benzoyl chloride in pyridine (48 hours at room temperature). Its structure was shown by its hydrolysis to *cis*-Δ^5-cholestene-3 : 4-diol, and by its preparation from this diol (0·5 g.) in dry pyridine (6 c.c.) and benzene (10 c.c.) by heating in a sealed tube at 70° for 2 hours with carbonyl chloride in toluene (8·8 c.c.; 12·5%). The cooled solution was poured into water and extracted with ether, and the extract washed with dilute hydrochloric acid and then sodium carbonate solution. Removal of the ether gave a crystalline residue, from which the carbonate (VI) (0·37 g.) was obtained by crystallisation from alcohol (charcoal).

The uncrystallisable residue from the above oxidation was hydrolysed with 5% methyl-alcoholic potash, and again gave Δ^4-cholestene-3 : 6-diol.

Oxidation of 3-O-*carbethoxycholesterol in acetic anhydride solution.* This was carried out with 3-*O*-carbethoxycholesterol (Robberecht, *loc. cit.*) (2·38 g.), the oxidation and working up being carried out as in the corresponding treatment of the carbomethoxy-compound. The crystalline material (0·86 g.) obtained by trituration with alcohol of the crude brown gum was separated, by fractional crystallisation from acetone, into less soluble, long, colourless needles, m. p. 163—163·5°, and more soluble rosettes of colourless elongated platelets (from alcohol), m. p. 121—122·5°. The higher-melting compound was shown to be 3-O-*carbethoxy*-4-*acetoxycholesterol* (V; R = Et, R′ = COMe) (Found: C, 73·6; H, 9·8. $C_{32}H_{52}O_5$ requires C, 74·4; H, 10·1%). It was unaffected by boiling acetic anhydride, and was hydrolysed by boiling 5% methyl-alcoholic potash to *cis*-Δ^5-cholestene-3 : 4-diol. This mixed ester was also prepared by the following two methods: (*a*) The diol (1 g.) was converted into 3-O-*carbethoxy*-4-*hydroxycholesterol* (V; R = Et, R′ = H) by treatment with ethyl chloroformate and pyridine as in the corresponding treatment with methyl chloroformate. The 3-monoester formed small, elongated, rectangular plates, m. p. 130·5—131° (Found: C, 76·0; H, 10·7. $C_{30}H_{50}O_4$ requires C, 76·0; H, 10·55%). Acetylation with boiling acetic anhydride (1 hour) gave 3-*O*-carbethoxy-4-acetoxycholesterol, m. p. 162·5—163°, identical with that obtained from the selenium dioxide oxidation. Benzoylation of the 3-monoester (200 mg.) with benzoyl chloride (1 c.c.) in pyridine (5 c.c.) (2 hours at 100°) gave 3-O-*carbethoxy*-4-*benzoyloxycholesterol*, colourless elongated platelets (from alcohol), m. p. 131—131·5° (Found: C, 76·4; H, 9·25. $C_{37}H_{54}O_5$ requires C, 76·8; H, 9·3%). The m. p. was strongly depressed by admixture with the monoester.

(*b*) The 4-monoacetate of *cis*-Δ^5-cholestene-3 : 4-diol was esterified with ethyl chloroformate in pyridine under the standard conditions (see above) and gave the same 3-*O*-carbethoxy-4-acetoxycholesterol.

The compound, m. p. 121—122·5°, isolated from the products of oxidation of 3-*O*-carbethoxycholesterol, gave on hydrolysis with boiling 5% methyl-alcoholic potash Δ^4-cholestene-3 : 6-diol, m. p. 256—257°. This product was evidently 3-O-*carbethoxy*-6-*acetoxy*-Δ^4-*cholesten*-3-*ol* (IV; R = Et) (Found: C, 74·6; H, 10·2. $C_{32}H_{52}O_5$ requires C, 74·4; H, 10·1%).

Oxidation of 3-O-*carbethoxycholesterol in acetic acid solution.* 3-*O*-Carbethoxycholesterol (4·28 g.) was oxidised with selenium dioxide (2 g.) as described for the corresponding experiment with the carbomethoxy-compound. The crude mixture of products was obtained by slow crystallisation, during 6 weeks, from acetic acid. Fractional crystallisation from acetone of the resulting solid gave (*a*) 3-*O*-carbethoxy-4-acetoxycholesterol, m. p. 163°, (*b*) the carbonate (VI), m. p. 173°; this was obtained by crystallisation from ligroin of the material from the acetone liquors of (*a*); (*c*) 3-*O*-carbethoxy-6-acetoxy-Δ^4-cholesten-3-ol, m. p. 115—117·5°, not depressed by the pure material, m. p. 121—122·5°. This was obtained by further crystallisation from acetone and ligroin, of the material from the liquors of (*b*).

B. *Rearrangement of* 3-*Monoesters* (VII) *of* cis-Δ^5-*Cholestene*-3 : 4-*diol.*—(*a*) A saturated solution of the 3-monoacetate (3 g.) in acetic acid at 90° was maintained at this temperature for an hour. The crystals which separated on cooling were collected; fractional crystallisation from methyl alcohol of these, and of the crystals obtained from the acetic acid liquors by vacuum concentration, gave the 4-monoacetate (IX; R = Me) (1·9 g.), m. p. 161—163°. Treatment of this with benzoyl chloride in pyridine gave the 4-acetate-3-benzoate, m. p. 165·5—166·5°, identical with a specimen prepared by acetylation of the 3-monobenzoate formed by selenium dioxide oxidation of cholesteryl benzoate (Rosenheim and Starling, J., 1937, 380).

(*b*) A solution of the 3-monoacetate (1 g.) in propionic acid (5 c.c.) was heated at 100° for an hour. The first crops of crystals obtained were largely unchanged 3-monoacetate. The more soluble material from the liquors was obtained as a gum which gave, with benzoyl chloride in pyridine, the above-mentioned 4-acetate-3-benzoate, m. p. 165·5—166·5°.

(*c*) A solution of 3-*O*-carbomethoxy-4-hydroxycholesterol (V; R = Me, R′ = H) (200 mg.) in glacial acetic acid (10 c.c.) and water (0·5 c.c.) was boiled for an hour. The product, after several recrystallisations from alcohol, gave the glycol carbonate (VI), m. p. 173°. When the experiment was carried out at 90°, some carbonate was formed but much of the carbomethoxy-compound was unchanged.

(*d*) The carbonate was also formed when a solution of the 3-*O*-carbomethoxy-compound (100 mg.) in propionic acid (10 c.c.) and water (0·5 c.c.) was boiled for an hour.

(*e*) A solution of 3-*O*-carbethoxy-4-hydroxycholesterol (400 mg.) in glacial acetic acid (20 c.c.) and water (1 c.c.) was boiled for 30 minutes. The glycol carbonate (180 mg.) was again isolated.

C. *Additional Experiments.—Action of methylmagnesium iodide on the carbonate* (VI). A solution of the carbonate (0·5 g.) in ether (20 c.c.) was added to ethereal methylmagnesium iodide (2 mols.), and the whole kept overnight in an atmosphere of dry hydrogen. The product was poured into ice-water and acidified with hydrochloric acid, and the ethereal extract washed, dried, and freed from solvent. The residue crystallised from alcohol in colourless needles, m. p. 77—78° after several recrystallisations from methyl alcohol. The m. p. was not depressed by admixture with Δ^4-cholestene, prepared by reduction of Δ^4-cholestene-3 : 6-diol (see below).

Reduction of 6(*β*)-*acetoxy*-Δ^4-*cholesten*-3-*one* (I). Sodium (5 g.) was added during 40 minutes to a boiling solution of the ketone (1 g.) (Ellis and Petrow, J., 1939, 1081) in amyl alcohol (40 c.c.). Boiling was continued for 3 hours, during which more amyl alcohol (20 c.c.) was added. The cooled reaction mixture was decomposed with water, the amyl alcohol layer separated, and the aqueous liquors extracted with ether. The ethereal extract was combined with the amyl

alcohol solution, and the whole washed and freed from solvents. The resulting pale yellow viscous residue could not be crystallised and was treated (48 hours at room temperature) with benzoyl chloride (4 c.c.) in pyridine (10 c.c.). The product was isolated in the usual way as a gum which, triturated with acetone, gave a solid. Recrystallisation from acetone–chloroform and then ethyl acetate gave 3(β) : 6(α)-cholestanediol dibenzoate (0·12 g.), m. p. 213—214·5°, alone or mixed with an authentic sample prepared from cholesterol α-oxide (Urushibara, *Bull. Chem. Soc. Japan*, 1941, **16**, 182). Hydrolysis of the dibenzoate gave the free diol, m. p. 218—219·5°.

Reduction of Δ⁴*-cholestene-3 : 6-diol.* Sodium (10 g.) was added during an hour to a boiling solution of the diol (2 g.) in amyl alcohol (100 c.c.), boiling being continued for 3 hours. The product, isolated as described in the preceding case, was an almost colourless gum, an alcoholic solution of which deposited long needles when cooled. Recrystallisation gave pure Δ⁴-cholestene (1·4 g.), m. p. 79—80°. The m. p. was depressed by admixture with coprostenone or Δ⁵-cholestene. Catalytic hydrogenation with palladium-black gave cholestane, m. p. 77—78°, not depressed by an authentic specimen of cholestane, of m. p. 79—80°.

Cholesteryl benzoate α- and β-oxides (compare Spring and Swain, J., 1939, 1356; Chakravorty and Levin, *J. Amer. Chem. Soc.*, 1942, **64**, 2317). A solution of monoperphthalic acid (24 g.) in ether (1 l.) was added dropwise during 90 minutes to a stirred solution of cholesteryl benzoate (40 g.) in ether (450 c.c.) and chloroform (300 c.c.), the temperature being kept at −5°. After 12 hours at 0° and 4 days at room temperature, the excess of peracid was extracted with sodium carbonate solution. The washed and dried ether–chloroform solution was evaporated, and the crystalline residue recrystallised several times from ethyl acetate, giving pure cholesteryl benzoate α-oxide (22 g.), m. p. 168°, hydrolysed to cholesterol α-oxide, m. p. 142—143°. The material from the ethyl acetate liquors was recrystallised repeatedly from ethyl acetate–methyl alcohol, giving cholesteryl benzoate β-oxide (10·5 g.), m. p. 150°. Hydrolysis gave the β-oxide.

Cholesterol α-oxide (1·8 g.) was obtained by oxidation of cholesterol (2 g.) with monoperphthalic acid.

Reduction of cholesterol oxides. This was carried out in the usual way with sodium and amyl alcohol. By treatment of the crude resinous product from the β-oxide with acetone there was obtained a small yield of cholestane-3(β) : 6(α)-diol. Benzoylation of the gum from the acetone liquors gave the dibenzoate of this diol.

The same diol (0·11 g.) was obtained by similar reduction of cholesterol α-oxide (1 g.).

Grateful acknowledgment is made to Professor J. W. Cook, F.R.S., for his continued and stimulating interest in this work, to the Donaldson Trustees for the award of a scholarship, and to Mr. J. M. L. Cameron, by whom the compounds were micro-analysed.

UNIVERSITY OF GLASGOW. [*Received, April 15th*, 1943.]

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119. *Union of Aryl Nuclei. Part VI. Reactions with* 1-*Aryl*-3 : 3-*dimethyltriazens.*

By J. ELKS and D. H. HEY.

1-Aryl-3 : 3-dimethyltriazens are prepared from aniline, *m*- and *p*-nitroaniline, anthranilic acid, methyl anthranilate, β-naphthylamine, 4-aminophthalimide, methyl 4-aminophthalate, and 5-aminoquinoline. Various reactions are described between these triazens and benzene, nitrobenzene, pyridine and 2-methoxynaphthalene, whereby union of the nuclei is effected according to the equation :

$$Ar{\cdot}N{:}N{\cdot}NMe_2 + RH + HCl \longrightarrow ArR + N_2 + NHMe_2{,}HCl$$

The yields obtained are frequently good for reactions of this type, which provide further examples of amphoteric or radical substitution.

IN previous communications (J., 1934, 1797, 1966; 1938, 108, 113, 699, 1386; 1940, 349, 355, 358, 372, 1279, 1284; etc.) on reactions which result in the union of aryl nuclei, yielding unsymmetrically substituted biaryls, considerable attention has been paid to the use of the diazo-hydroxides (Gomberg reaction) and the nitroso-acylarylamines. Some modifications of these reactions have recently been described in a patent specification (I.G. Farb. Akt., B.P. 513,846; cf. also U.S.P. 2,280,504), in which it is shown that water-insoluble or sparingly soluble metallic salt derivatives (*e.g.*, zinc chloride compounds) of diazo-compounds, usually in presence of aluminium or ferric chloride and free acid, react with a second component which comprises a wide variety of aromatic derivatives (excluding hydroxy- and amino-compounds). As a further improvement it is shown that the diazo-compound may be prepared *in situ* by means of nitrous gases in presence of the second component. Water-insoluble diazo-derivatives are also prepared by the action of non-coupling primary or secondary amines on the diazo-compound, thus giving rise to substituted triazens, and of particular interest are the 1-aryl-3 : 3-dialkyltriazens which form the subject of the present communication. From the numerous examples given in the specification it is clear that all these modifications conform to the general principle of "amphoteric substitution" (Grieve and Hey, J., 1934, 1797, 1966) or "radical substitution" (Wheland, *J. Amer. Chem. Soc.*, 1942, **64**, 900), which has been shown to be characteristic of all reactions of this type.

1-Aryl-3 : 3-dimethyltriazens are prepared, usually in excellent yield, by the addition of an aqueous solution of the diazotised base to aqueous dimethylamine in the presence of sodium carbonate. The specification cited above refers in particular to 1-phenyl-3 : 3-dimethyltriazen, 1-(3′ : 4′-dichlorophenyl)-3 : 3-dimethyltriazen, and 1-(3′ : 4′-dimethylphenyl)-3 : 3-dimethyltriazen, prepared from aniline, 3 : 4-dichloroaniline and *o*-4-xylidine respectively. Such triazens, which may be liquids or solids, are stable in neutral or alkaline media but decompose into the diazo- and the dimethylamine salt in presence of acid. They may therefore be regarded as stabilised diazo-compounds and, as such, compounds of this type have found considerable employment in the dye industry (see Saunders, "The Aromatic Diazo Compounds," pp. 135—138). In order to form the biaryl the triazen is dissolved in an excess of the second component, and the solution heated, usually at 90—100°, while a slow current of dry hydrogen chloride (or other acidic reagent) is introduced. Under these conditions the biaryl is formed with evolution of nitrogen according to the equation :

$$Ar{\cdot}N{:}N{\cdot}NMe_2 + C_6H_5R + HCl \longrightarrow Ar{\cdot}C_6H_4R + N_2 + NHMe_2{,}HCl$$

This reaction possesses two advantages over other methods of biaryl formation in that (*a*) in contrast to the Gomberg reaction it is effected in a homogeneous medium, and (*b*) in contrast to the nitrosoacylarylamine method it is effected at an elevated temperature, which therefore permits the use of a wider range of compounds as second components by including those which are solid at the ordinary temperature but liquid at or about 90°.

Dimethyltriazens have now been prepared from aniline, *p*-nitroaniline, *m*-nitroaniline, methyl anthranilate, anthranilic acid, β-naphthylamine, 4-aminophthalimide, methyl 4-aminophthalate, and 5-aminoquinoline, and as second components benzene, nitrobenzene, 2-methoxynaphthalene and pyridine have been used. Of these triazens, 1-phenyl-3 : 3-dimethyltriazen has been described by Baeyer and Jaeger (*Ber.*, 1875, **8**, 148) and by Heusler (*Annalen*, 1890, **260**, 249). Reactions have been carried out in the presence of hydrogen chloride and in some cases of glacial acetic acid, and in many cases the yields of biaryl are surprisingly good for reactions of this type. No examples of the use of pyridine as second component are contained in the patent specification. The results of these reactions are summarised in the following table :

No.	Base used for preparation of triazen.	Second component.	Decomposing agent.	Biaryl.	Yield of biaryl, %.
1	Aniline	Benzene	HCl	Diphenyl	25
2	,,	,,	AcOH	,,	37
3	,,	Nitrobenzene	HCl	2- and 4-Nitrodiphenyl	35
4	,,	Pyridine	,,	α-, β-, and γ-Phenylpyridine	51
5	*p*-Nitroaniline	Benzene	,,	4-Nitrodiphenyl	52
6	,,	Pyridine	,,	α-, β-, and γ-4-Nitrophenylpyridine	50
7	*m*-Nitroaniline	Benzene	,,	3-Nitrodiphenyl	53
8	,,	,,	AcOH	—	0
9	Methyl anthranilate	2-Methoxynaphthalene	HCl	Methyl 2-methoxy-1-phenylnaphthalene-2′-carboxylate	25
10	,, ,,	,, ,,	AcOH	,, ,, — ,, ,,	29
11	Anthranilic acid	Benzene	HCl	—	0
12	β-Naphthylamine	,,	AcOH	2-Phenylnaphthalene	36
13	,,	Pyridine	HCl	2-Pyridylnaphthalenes	41
14	5-Aminoquinoline	Benzene	,,	5-Phenylquinoline	13
15	4-Aminophthalimide	,,	,,	4-Phenylphthalimide	v. small
16	,,	Pyridine	,,	4-Pyridylphthalimides	49
17	Methyl 4-aminophthalate	Benzene	,,	Methyl 4-phenylphthalate	66

In the formation of diphenyl the replacement of hydrogen chloride by glacial acetic acid resulted in an increased yield, but in other cases this change effected little improvement in yield and in some instances acetic acid proved to be useless as a decomposing agent, for example, in the reaction of 1-m-*nitrophenyl*-3 : 3-*dimethyltriazen* with benzene. This observation appears to indicate that the nitro-group exerts a stabilising influence on the triazen towards acids. Both 1-m- and 1-p-*nitrophenyl*-3 : 3-*dimethyltriazen* gave nitrodiphenyls in comparatively high yield and with a notable absence of tar. The use of the triazen reaction with a second component which is solid at room temperature is exemplified in the preparation of methyl 2-methoxy-1-phenylnaphthalene-2′-carboxylate, an intermediate for the preparation of 3′-hydroxy*meso*benzanthrone. This ester had been obtained in 18% yield by Heilbron, Hey, and Wilkinson (J., 1938, 699) by the action of diazotised methyl anthranilate on a chloroform solution of 2-methoxynaphthalene. Since 2-methoxynaphthalene liquifies at 72°, the use of the solvent can be dispensed with in the triazen method. The quantity of 2-methoxynaphthalene used in these experiments was small (about 2 mols.) compared with the much greater excess (15—20 mols.) used in reactions with benzene or pyridine, but in addition to the improved yield the method of working-up was considerably easier in the triazen method. In the reaction between 1-β-*naphthyl*-3 : 3-*dimethyltriazen* and pyridine a mixture of 2-pyridylnaphthalenes was obtained, from which three *isomerides* were separated by fractional crystallisation of the picrates. One of these picrates was identical with a product prepared by Dr. J. W. Haworth by the action of aqueous naphthalene-β-diazonium chloride on pyridine, and the same product was also prepared by Mr. C. W. Pritchett from the reaction of nitrosoaceto-β-naphthalide with pyridine. In both of these reactions the yields were small. In the reaction between the dimethyltriazen from 5-aminoquinoline and benzene a high proportion of 5-chloroquinoline was formed in addition to 5-*phenylquinoline*. The *dimethyltriazen* prepared from 4-aminophthalimide with pyridine gave a mixture of 4-*pyridylphthalimides*, which appeared to be identical with a similar product previously prepared by Dr. J. W. Haworth from aqueous diazotised 4-aminophthalimide and pyridine.

Both 4-aminophthalimide and methyl 4-aminophthalate were also submitted to the Gomberg reaction and its sodium acetate modification previously reported (Elks, Haworth, and Hey, J., 1940, 1284). In the reaction between diazotised 4-aminophthalimide and benzene in presence of sodium hydroxide no 4-phenylphthalimide could be isolated, probably owing to the solubility of the phthalimide in the aqueous alkaline layer (cf. Grieve and Hey, J., 1938, 108). When sodium acetate replaced sodium hydroxide, some 4-phenylphthalimide was formed but only in minute yield. On the other hand, diazotised methyl 4-aminophthalate and benzene in presence of sodium hydroxide gave methyl 4-phenylphthalate in 34% yield, but when sodium acetate replaced sodium hydroxide in this reaction the yield of methyl 4-phenylphthalate was increased to 52% (cf. Butterworth, Heilbron, Hey, and Wilkinson, J., 1938, 1386).

Experimental.

Preparation of 1-Aryl-3 : 3-dimethyltriazens.—Except when otherwise stated, the following general method was used for the preparation of the triazens: An aqueous solution of the diazonium chloride, prepared in the usual manner from the aromatic amine (1 mol.), was added slowly from a cooled dropping-funnel to a cooled stirred mixture of aqueous dimethylamine (33%; 160 g.) and an excess of 30% aqueous sodium carbonate over that required for the neutralisation of the acid. Stirring was continued for ½ hour, and the separated triazen then either extracted with ether or benzene or, if solid, collected by filtration. The extract was dried over caustic potash and after removal of the solvent the residual triazen was distilled under reduced pressure. The solid triazens were purified by direct crystallisation.

1-*Phenyl*-3 : 3-*dimethyltriazen.*—The triazen was prepared in 93% yield. It boiled at 125—127°/19 mm. Heusler (*loc. cit.*) recorded b. p. 113—114°/12 mm.

Reactions with benzene. (i) The triazen (20 g.), dissolved in benzene (200 c.c.), was refluxed in a flask fitted with a gas inlet tube and a calcium chloride guard-tube at the end of the condenser. A slow stream of dry hydrogen choride was passed through. When reaction was complete, hot water was added to remove dimethylamine hydrochloride and the benzene layer was separated, dried (sodium sulphate), and distilled. Evaporation to dryness of the aqueous layer gave dimethylamine hydrochloride (10 g.). After removal of most of the benzene the residue was fractionated at atmospheric pressure and chlorobenzene (2·4 g.) was collected at 130—132°, which was identified by nitration to give *p*-chloronitrobenzene, m. p. and mixed m. p. 83°. On further distillation under reduced pressure diphenyl (5·1 g.) was obtained in 25% yield, m. p. 69—70° after crystallisation from alcohol. A tarry residue (5·1 g.) remained.

(ii) In a second experiment with the triazen (17·6 g.) and benzene (175 c.c.), glacial acetic acid (25 g.) was added slowly in place of hydrogen chloride. The mixture was refluxed over-night, washed with water, and the benzene layer separated, dried, and distilled as above. Diphenyl (6·8 g.) was obtained in 37% yield, m. p. 69—70° after crystallisation from alcohol.

Reaction with nitrobenzene. Dry hydrogen chloride was passed into a solution of the triazen (23 g.) in nitrobenzene (300 c.c.) heated on the steam-bath. When evolution of nitrogen had ceased, the mixture was washed with hot water, and the nitrobenzene layer dried and distilled under reduced pressure. After removal of the nitrobenzene a mixture of nitrodiphenyls (10·6 g.) was collected at 180—200°/24 mm. in 35° yield. Crystallisation of the mixture from alcohol yielded 4-nitrodiphenyl, m. p. 112—113°, and evaporation of the mother-liquors to dryness and crystallisation of the residual oil from light petroleum (b. p. 40—60°) gave 2-nitrodiphenyl, m. p. 37—38°.

Reaction with pyridine. Dry hydrogen chloride was passed into a solution of the triazen (23 g.) in pyridine (250 c.c.) heated on the steam-bath. When reaction was complete, the mixture was allowed to cool, and the resulting solid mass treated with an excess of aqueous sodium hydroxide. The pyridine layer was separated, the aqueous alkaline layer extracted with more pyridine, and the combined pyridine extracts dried (caustic potash) and distilled. After removal of pyridine further distillation was continued under reduced pressure. Redistillation of the fraction collected above 80°/20 mm. gave a mixture of phenylpyridines (12·1 g.) at 140—150°/16 mm. in 51% yield. Fractional crystallisation of the picrates from acetone, as described by Haworth, Heilbron, and Hey (J., 1940, 349), gave α-phenylpyridine picrate, m. p. 173—175°, β-phenylpyridine picrate, m. p. 156—158°, and γ-phenylpyridine picrate, m. p. 194—196°, all undepressed by authentic specimens.

1-p-*Nitrophenyl*-3 : 3-*dimethyltriazen*, prepared in 95% yield, separated from light petroleum (b. p. 60—80°) or benzene in reddish needles, m. p. 144—145° (Found: C, 49·6; H, 5·3. $C_8H_{10}O_2N_4$ requires C, 49·5; H, 5·2%).

Reaction with benzene. A boiling solution of the triazen (15 g.) in benzene (250 c.c.) was treated with dry hydrogen chloride as described above in the preparation of diphenyl (method i). Crystallisation of the solid residue, obtained on removal of the benzene, from alcohol gave 4-nitrodiphenyl (8·0 g.) in yellow needles, m. p. 114°, in 52% yield.

Reaction with pyridine. Dry hydrogen chloride was passed for 16 hours into a solution of the triazen (25 g.) in pyridine (250 c.c.) heated on the steam-bath. When the reaction was complete, excess of aqueous sodium hydroxide was added, and the pyridine layer separated. The aqueous layer was further extracted with benzene and the combined pyridine and benzene extracts were distilled in steam to remove the solvents. Towards the end of this distillation a small quantity of *p*-chloronitrobenzene, m. p. 82—83°, collected in the condenser. The brown solid non-volatile residue (18 g.) was collected, dried, and distilled in a vacuum, a solid mixture of 4-nitrophenylpyridines (13·0 g.) being collected at 170—190°<1 mm. (yield, 50%). Separation of the isomerides by the method of Forsyth and Pyman (J., 1926, 2912) gave α-4-nitrophenylpyridine (m. p. and mixed m. p. 129—130°) and β-4-nitrophenylpyridine (m. p. and mixed m. p. 146—147°). The γ-4-nitrophenylpyridine was not obtained in a pure state.

1-m-*Nitrophenyl*-3 : 3-*dimethyltriazen* crystallised from light petroleum (b. p. 60—80°) in yellow prisms, m. p. 99—100° (Found: C, 49·7; H, 5·0. $C_8H_{10}O_2N_4$ requires C, 49·5; H, 5·2%).

Reaction with benzene. Dry hydrogen chloride was passed into a boiling solution of the triazen (60 g.) in benzene (650 c.c.), and the product worked up as in the preparation of diphenyl (method i). After removal of benzene, further distillation under reduced pressure gave 3-nitrodiphenyl (32·6 g.) in 53% yield as a yellow crystalline mass, m. p. 60° after crystallisation from alcohol. In an attempt to use glacial acetic acid in place of hydrogen chloride the greater bulk of the triazen was recovered unchanged even after boiling under reflux over-night.

1-o-*Carbomethoxyphenyl*-3 : 3-*dimethyltriazen*, prepared from diazotised methyl anthranilate, distilled at 180—182°/18 mm. as a pale yellow liquid, which, however, was not obtained analytically pure (Found: C, 59·0; H, 6·6. $C_{10}H_{13}O_2N_3$ requires C, 57·9; H, 6·3%).

Reaction with 2-methoxynaphthalene. Dry hydrogen chloride was passed into a solution of the crude triazen (20 g.) in molten 2-methoxynaphthalene (30 g.) heated on the water-bath. When evolution of nitrogen had ceased, the resulting cold solid mass was extracted with benzene and filtered from dimethylamine hydrochloride. After evaporation of the benzene the residue was distilled in a vacuum. The excess of 2-methoxynaphthalene was collected at 140—150°/12 mm. and methyl 2-methoxy-1-phenylnaphthalene-2′-carboxylate (7·1 g.) then distilled at 220—240°/12 mm. as a yellow oil (yield, 25%). Hydrolysis with alcoholic potassium hydroxide gave 2-methoxy-1-phenylnaphthalene-2′-carboxylic acid, m. p. and mixed m. p. 216—218°. In a second experiment with the same quantities the slow addition of glacial acetic acid (24 g.) replaced the hydrogen chloride. Heating on the water-bath was continued over-night. On working up the product as before, methyl 2-methoxy-1-phenylnaphthalene-2′-carboxylate (8·2 g.) was collected at 200°/<1 mm. (yield, 29%).

1-o-*Carboxyphenyl*-3 : 3-*dimethyltriazen* was prepared from diazotised anthranilic acid by the general method outlined above, but when the reaction was complete the mixture was made slightly acid with dilute acetic acid, and the precipitated triazen filtered off and dried. Crystallisation from benzene–ligroin gave long white needles (24 g.; yield, 74%), m. p. 124—126° (decomp.) (Found: C, 56·2; H, 5·8; N, 21·6. $C_9H_{11}O_2N_3$ requires C, 55·9; H, 5·7; N, 21·7%).

Reaction with benzene. Dry hydrogen chloride was passed into a boiling solution of the triazen (6·2 g.) in benzene (50 c.c.). The resulting solution was extracted with aqueous sodium hydroxide. Acidification of the alkaline solution deposited an acid, which on crystallisation from water gave *o*-chlorobenzoic acid (1·9 g.), m. p. and mixed m. p. 133—135°.

1-*β-Naphthyl*-3 : 3-*dimethyltriazen* crystallised from light petroleum (b. p. 60—80°), with addition of charcoal, in reddish prisms, m. p. 57—58°, the colour of which was largely removed by adsorption of alumina (Found : C, 73·1; H, 6·6. $C_{12}H_{13}N_3$ requires C, 72·3; H, 6·6%).

Reaction with benzene. Addition of glacial acetic acid (10 c.c.) to a boiling solution of the triazen (10 g.) in benzene (100 c.c.) and subsequent treatment as described in the preparation of diphenyl (method ii) gave a residue, which was distilled in a high vacuum. 2-Phenylnaphthalene (3·7 g.) was obtained, which after crystallisation from alcohol melted at 101—102°, both alone and on admixture with an authentic specimen (yield, 36%).

Reaction with pyridine. Dry hydrogen chloride was passed into a stirred solution of the triazen (20 g.) in pyridine (200 c.c.) heated on the steam-bath. The product was worked up as in the preparation of the nitrophenylpyridines. The water was decanted from the non-steam-volatile tarry solid, which was then dissolved in benzene. The benzene extract was dried (potassium hydroxide), the benzene removed, and the residue distilled in a high vacuum. A mixture of 2-pyridylnaphthalenes (8·4 g.) was collected at 185—205°/<1 mm. as a yellow oil, which solidified (yield, 41%). The product (8 g.), dissolved in hot ethyl alcohol, was added to a hot concentrated alcoholic solution of picric acid (9·5 g.). After boiling for ½ hour a solid picrate separated, which was filtered off (14 g.) and fractionally crystallised from acetone. Three isomeric *picrates* were isolated as follows : (*a*) yellow needles, m. p. 199—200° (Found : N, 13·1. $C_{15}H_{11}N,C_6H_3O_7N_3$ requires N, 12·9%); (*b*) yellow needles, m. p. 177—178° (Found : N, 12·8%); (*c*) yellow prisms, m. p. 216—217° (Found : N, 13·3%). The isomeride (*c*) appeared to be present to only a small extent. The free *base* generated from picrate (*a*) was obtained in small white needles, m. p. 99—100° after crystallisation from light petroleum (b. p. 40—60°) (Found : C, 87·8; H, 5·4. $C_{15}H_{11}N$ requires C, 87·8; H, 5·4%). The free *base* generated from picrate (*b*) crystallised from light petroleum (b. p. 40—60°) in clusters of needles, m. p. 69—70° (Found : C, 88·1; H, 6·4%). The m. p. of picrate (*b*) was undepressed on admixture with the compounds prepared by Dr. J. W. Haworth and Mr. C. W. Pritchett respectively as described below.

Preparation of 2-Pyridylnaphthalenes from Diazotised β-Naphthylamine (With J. W. Haworth).—The filtered diazonium chloride, prepared in the usual manner from β-naphthylamine (70 g.), was added during 2 hours to pyridine (500 c.c.) stirred at 20—25°. After standing overnight, the mixture was poured into water (2 l.) and the dark-coloured solid which separated was filtered off and dried (70 g.). A portion of this material (15 g.), which appeared to consist largely of azo by-products, was refluxed with acetic acid (400 c.c.), to which a solution of stannous chloride (100 g.) in concentrated hydrochloric acid (100 c.c.) was gradually added. The filtered solution was made alkaline and extracted with ether. The oil obtained on removal of the solvent was extracted with hot 5N-hydrochloric acid (100 c.c.). The solid hydrochloride which separated on cooling gave β-naphthylamine on basification, whereas basification of the hydrochloric acid filtrate gave a yellow solid (m. p. 35—45°), which was purified by sublimation in a vacuum. After removal of a small quantity of β-naphthylamine, a mixture of *2-pyridylnaphthalenes* was collected as a pale yellow solid (m. p. 40—50°), readily soluble in dilute acids and most organic solvents. The crude picrate, prepared in the normal manner in alcoholic solution, melted at 150—165°, but further crystallisation from acetone raised the m. p. to 177—180° (Found : C, 58·2; H, 3·2. $C_{15}H_{11}N,C_6H_3O_7N_3$ requires C, 58·1; H, 3·0%).

Preparation of 2-Pyridylnaphthalenes from Nitrosoaceto-β-naphthalide (With C. W. Pritchett).—Freshly prepared nitrosoaceto-β-naphthalide (20 g.), obtained by the nitrosyl chloride method described by Hey and Lawton (J., 1940, 378), was added in small portions during 20 minutes to vigorously stirred pyridine (150 c.c.). The solution became warm, but excessive heating was prevented by cooling in ice. Stirring was continued for ½ hour and evolution of nitrogen had then practically ceased. The solution was warmed to ensure completion of the reaction, and the excess of pyridine then removed by distillation with steam. A small quantity of naphthalene (0·3 g.) separated from the steam distillate. The dark red, non-volatile oil was extracted with benzene (400 c.c.) and dried. After removal of the solvent the residue was distilled at 10^{-3} mm. The distillate (5 g.) in benzene was purified by chromatographic adsorption, and the elutriate treated with alcoholic picric acid. Crystallisation of the product from acetone gave a 2-pyridylnaphthalene picrate, m. p. 177—179°.

1-(*5′-Quinolyl*)-3 : 3-*dimethyltriazen*.—This was obtained from diazotised 5-aminoquinoline in almost quantitative yield in crude form (m. p. 30—40°), but attempts to effect further purification by crystallisation were unsuccessful and an analytically pure specimen was not obtained.

Reaction with benzene. Dry hydrogen chloride was passed into a boiling solution of the crude triazen (10 g.) in benzene (100 c.c.), the mixture made alkaline with aqueous sodium hydroxide and filtered, and the benzene layer separated. The solvent was removed from the dried extract (sodium sulphate), and the residue distilled in a vacuum. Two fractions were obtained : (*a*) b. p. 90°/<1 mm. (2·9 g.), and (*b*) b. p. 160—180°/<1 mm. (1·3 g.). The former was a colourless liquid consisting of 5-chloroquinoline, part of which was converted into the *picrate*, m. p. 220—223° (from acetone) (Found : N, 14·0. $C_9H_6NCl,C_6H_3O_7N_3$ requires N, 14·3%), and part into the oxalate, which separated from alcohol in white needles, m. p. 144—145° (Found : C, 57·6; H, 3·7. Calc. for $2C_9H_6NCl,C_2H_2O_4$: C, 57·6; H, 3·4%). Claus and Kayser (*J. pr. Chem.*, 1893, **48**, 270) recorded m. p. 145° for the oxalate of 5-chloroquinoline. Fraction (*b*) solidified and after crystallisation from aqueous alcohol *5-phenylquinoline* was obtained in white needles, m. p. 82—83° (yield, 13%) (Found : C, 88·0; H, 5·6. $C_{15}H_{11}N$ requires C, 87·8; H, 5·4%). The *picrate*, formed in the usual manner, separated from alcohol in small yellow crystals, m. p. 210—211° (Found : N, 12·9. $C_{15}H_{11}N,C_6H_3O_7N_3$ requires N, 12·9%).

1-*Phenyl*-3 : 3-*dimethyltriazen*-3′ : 4′-*dicarboxyimide*.—The filtered diazonium sulphate prepared from 4-aminophthalimide (43 g.) (Levy and Stephen, J., 1931, 80) was added slowly to a mixture of aqueous dimethylamine (26·2%; 50 g.) and excess of aqueous sodium carbonate. The precipitated solid was collected and dried. Crystallisation from pyridine gave 1-*phenyl*-3 : 3-*dimethyltriazen*-3′ : 4′-*dicarboxyimide* (40 g.), m. p. 251—253° (decomp.) (yield, 69%) (Found : C, 54·8; H, 4·8; N, 25·5. $C_{10}H_{10}O_2N_4$ requires C, 55·0; H, 4·6; N, 25·7%).

Reaction with benzene. Dry hydrogen chloride was passed for 12 hours into a vigorously stirred, boiling suspension of the triazen (19 g.) in benzene (1 l.). The solid collected (15 g.) was unchanged triazen. Evaporation of the benzene solution almost to dryness deposited a solid (1·9 g.), which was purified by vacuum sublimation. Subsequent crystallisation from alcohol gave 4-phenylphthalimide, m. p. 200—201° alone and mixed with an authentic specimen.

Reaction with pyridine. Dry hydrogen chloride was passed into a stirred solution of the triazen (18·8 g.) in pyridine (200 c.c.) heated on the steam-bath, water added, and the resulting precipitate collected (m. p. >300°). Solid sodium acetate was added to the filtrate, and the resulting precipitate collected (9·5 g.), m. p. 210—215°. After sublimation in a vacuum a mixture of *4-pyridylphthalimides* was obtained in 49% yield, m. p. 232—242° (Found : C, 69·9; H, 3·9; N, 12·6. $C_{13}H_8O_2N_2$ requires C, 69·6; H, 3·6; N, 12·5%).

Preparation of 4-Pyridylphthalimides from Diazotised 4-Aminophthalimide (With J. W. Haworth).—The filtered diazonium sulphate, prepared from 4-aminophthalimide (24 g.), was added to pyridine (200 c.c.) at 40—50° during 2 hours. After a further ½ hour's heating, the mixture was poured into water (1500 c.c.). The yellow solid which separated was collected, dried (17 g.; yield, 54%; m. p. 205—220°), and purified by vacuum sublimation. Crystallisation from alcohol gave a mixture of *4-pyridylphthalimides*, m. p. 238—245° (Found : C, 69·6; H, 3·9. $C_{13}H_8O_2N_2$ requires C, 69·6; H, 3·6%).

Methyl 1-*Phenyl*-3 : 3-*dimethyltriazen*-3′ : 4′-*dicarboxylate*.—This *triazen*, prepared from diazotised methyl 4-amino-

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